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United States Patent [19]

Yamasaki et al.

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[45] Date of Patent: Dec. 26, 2000

[54] **BENZIMIDAZOLE DERIVATIVES**

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[73] Assignee: **Fujisawa Pharmaceutical Co., Ltd.**, Osaka, Japan

[21] Appl. No.: **09/091,997**

[22] PCT Filed: **Dec. 27, 1996**

[86] PCT No.: **PCT/JP96/03858**

§ 371 Date: **Nov. 2, 1998**

§ 102(e) Date: **Nov. 2, 1998**

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PCT Pub. Date: **Jul. 10, 1997**

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Oct. 8, 1996 [JP] Japan 8-287676

[51] **Int. Cl.**[7] **C07D 235/08**; C07D 235/10; C07D 401/06; C07D 405/06; A61K 31/415; A61K 31/44

[52] **U.S. Cl.** **548/309.4**; 514/307; 514/308; 514/309; 514/310; 514/311; 514/312; 514/313; 514/314; 514/394; 546/139; 546/141; 546/142; 546/143; 546/146; 546/149; 546/151; 546/153; 546/155; 546/156; 546/157; 546/159; 546/162; 546/167; 548/304.4; 548/307.1; 548/308.4; 548/309.7

[58] **Field of Search** 514/307, 309, 514/310, 311, 312, 313, 314, 394; 546/139, 141, 142, 143, 146, 149, 151, 152, 153, 155, 156, 157, 159, 162, 167; 548/304.4, 309.4, 309.7, 307.1, 308.4

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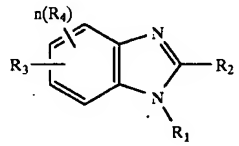
Primary Examiner—Floyd D. Higel
Attorney, Agent, or Firm—Fish & Richardson P.C.

[57] **ABSTRACT**

Novel benzimidazole derivatives represented by the formula (I):

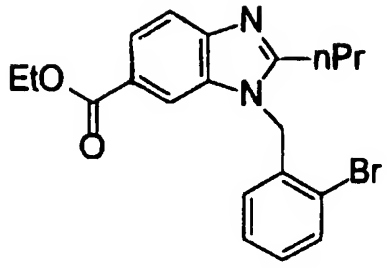
(I)



wherein R_3 is a carboxyl group, a esterified carboxyl group, an amidated carboxyl group, an amino group, an amido group, or a sulfonyl group, or their pharmaceutically acceptable salts. Because of their blood sugar-depressing effect or PDE5 inhibitory effect, these compounds or salts thereof are useful as medicines for treating impaired glucose tolerance, diabetes, diabetic complications, syndrome of insulin resistance, hyperlipidemia, atherosclerosis, cardiovascular disorders, hyperglycemia, or hypertension; or stenocardia, hypertension, pulmonary hypertension, congestive heart failure, glomerulopathy, tubulointerstitial disorders, renal failure, atherosclerosis, angiostenosis, distal angiopathy, cerebral apoplexy, chronic reversible obstructions, allergic rhinitis, urticaria, glaucoma, diseases characterized by enteromotility disorders, impotence, diabetic complications, nephritis, cancerous cachexia, or restenosis after PTCA.

6 Claims, 58 Drawing Sheets

FIG. 1



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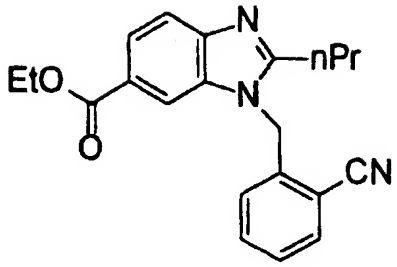

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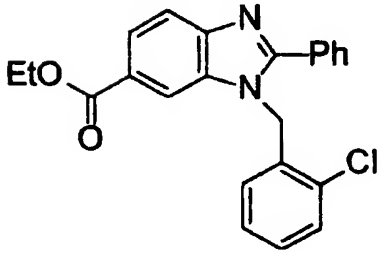

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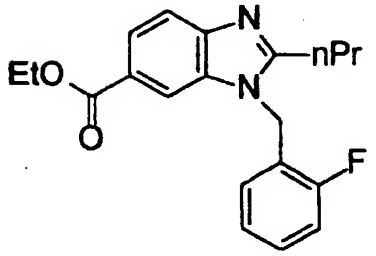

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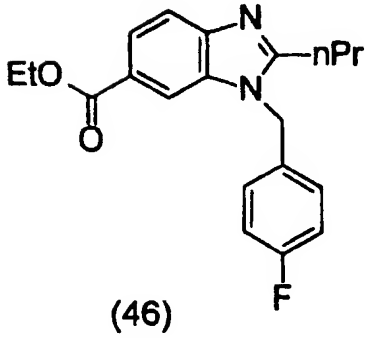

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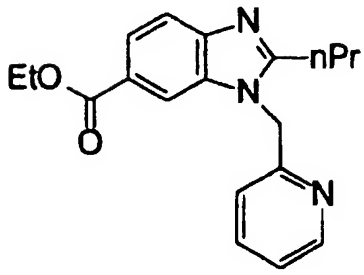
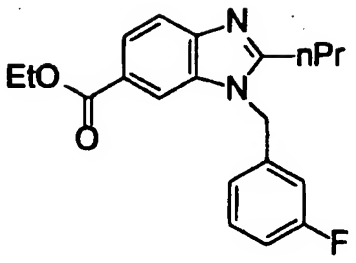


(47)

FIG. 2



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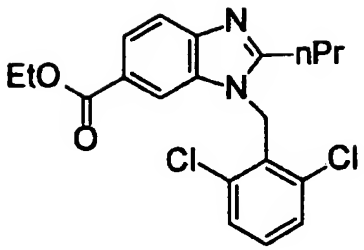

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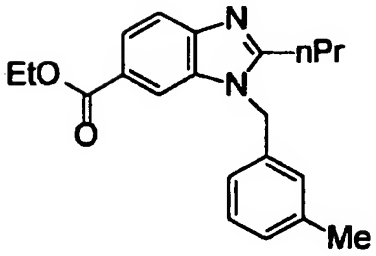

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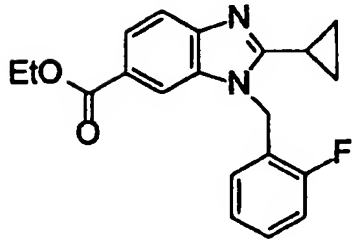

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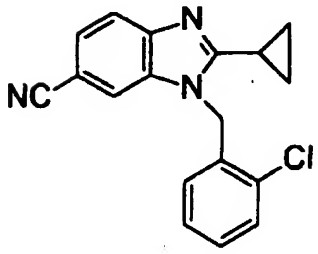

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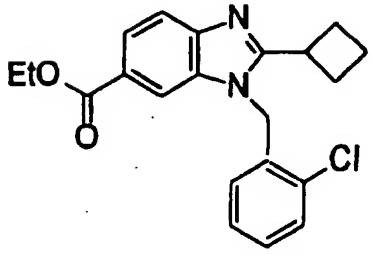

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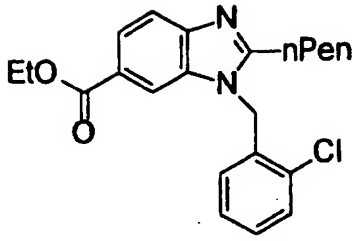
FIG. 3



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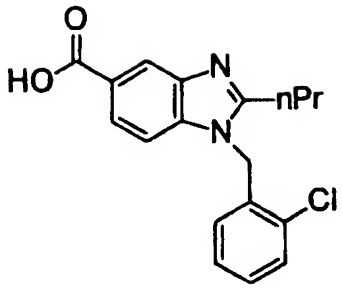

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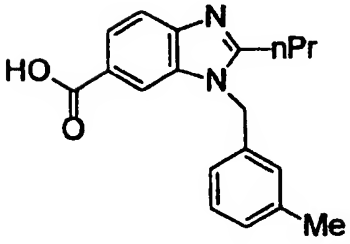

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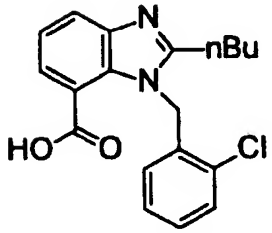

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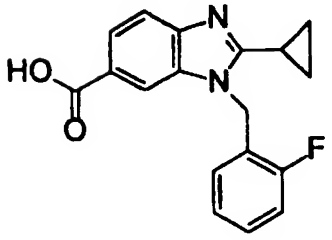

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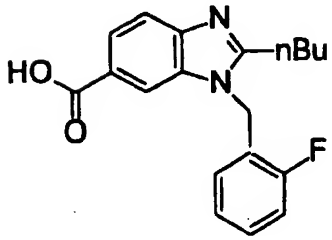

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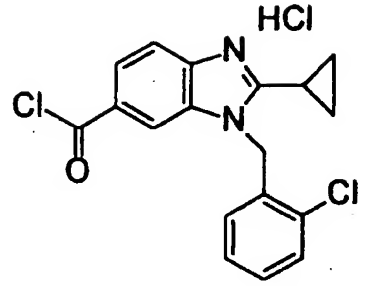

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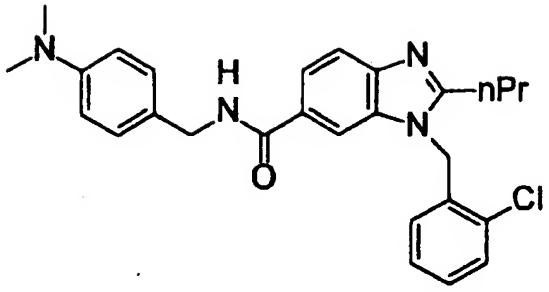

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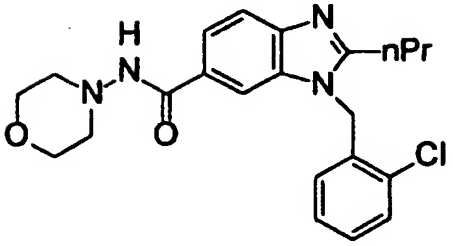

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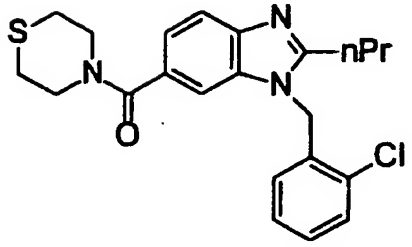

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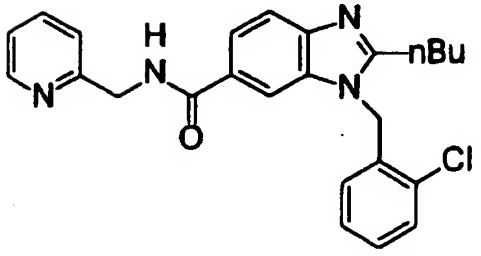

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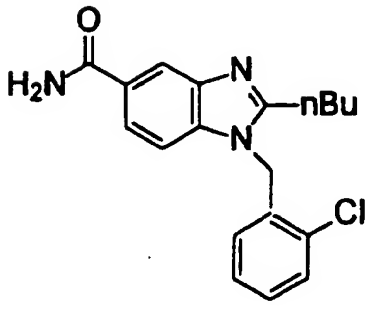

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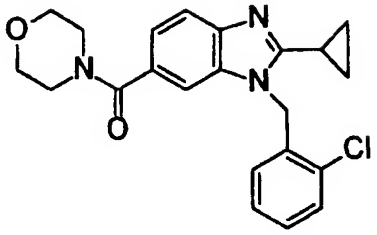
FIG. 5



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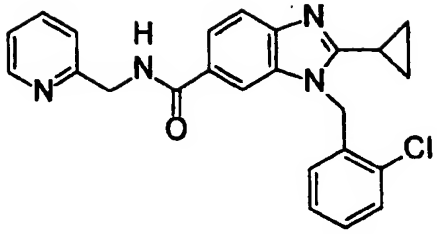

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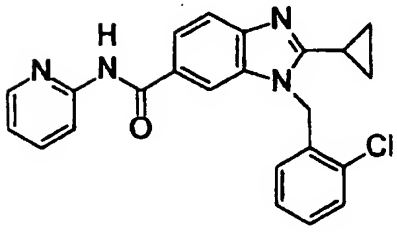

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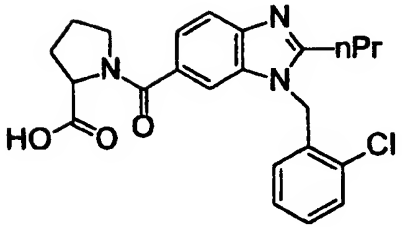

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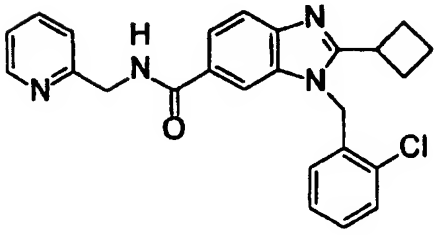

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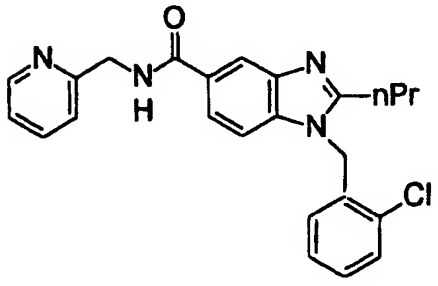

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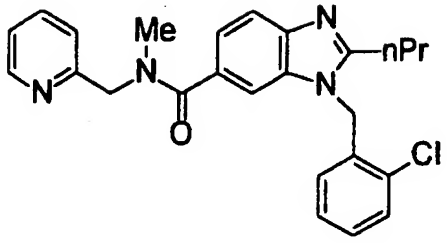
FIG. 6



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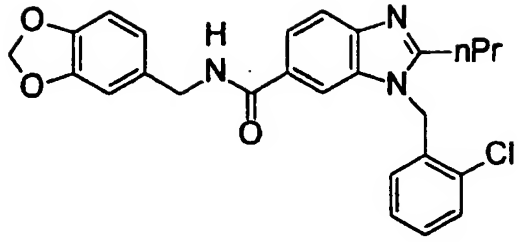

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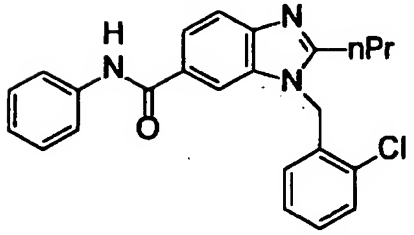

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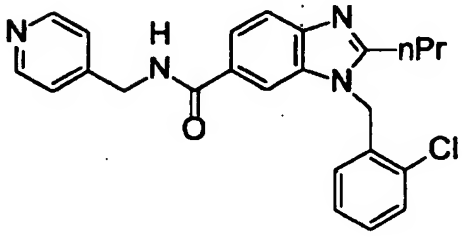

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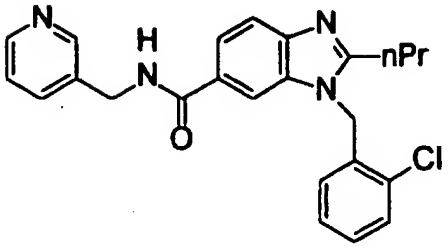

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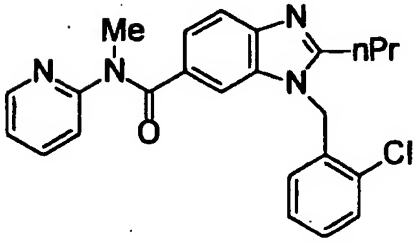

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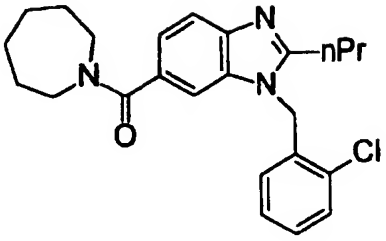

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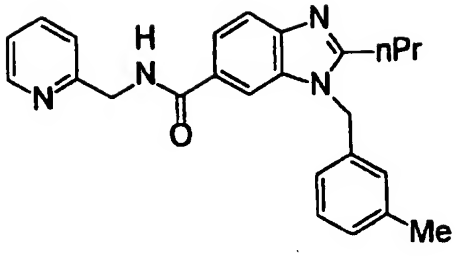

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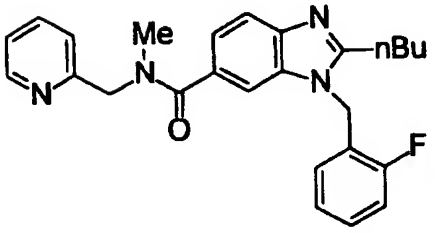

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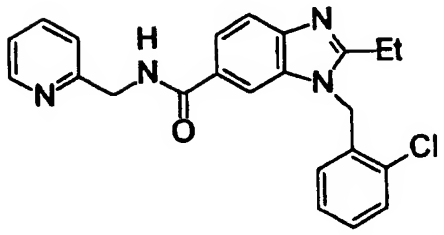

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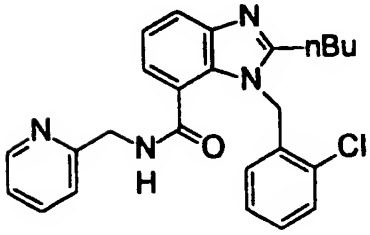

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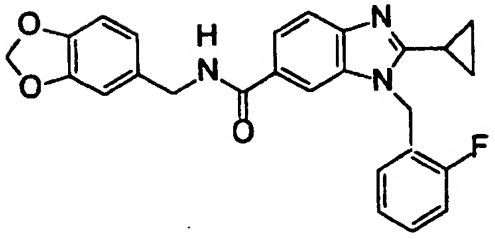

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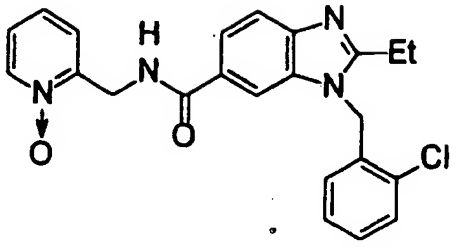
FIG. 8



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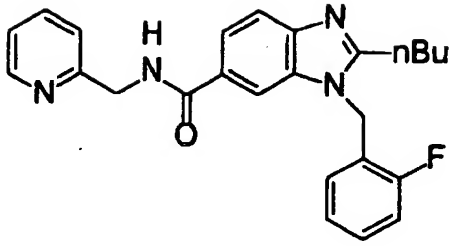

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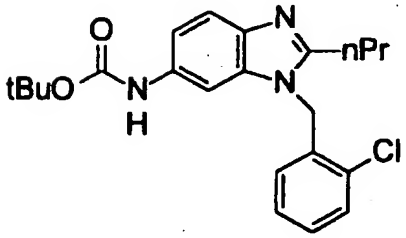

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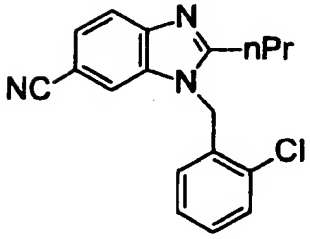

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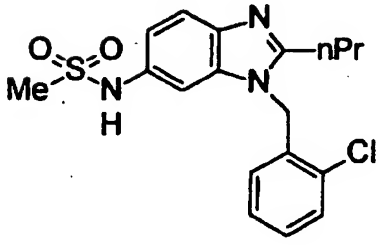

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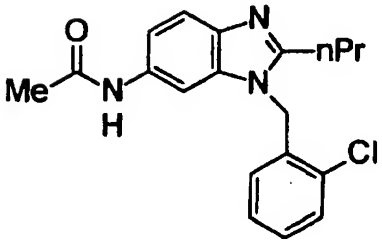
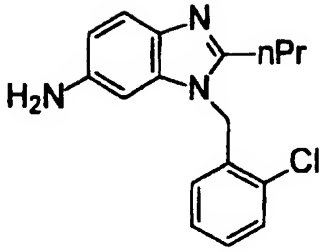


(89)

FIG. 9



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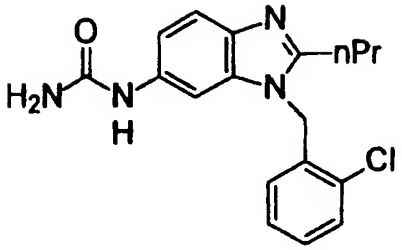

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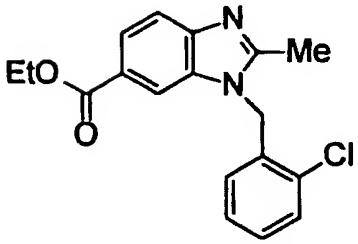

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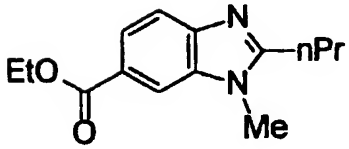
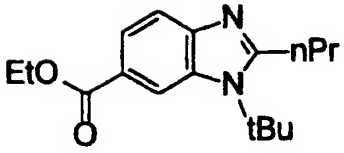


(93)



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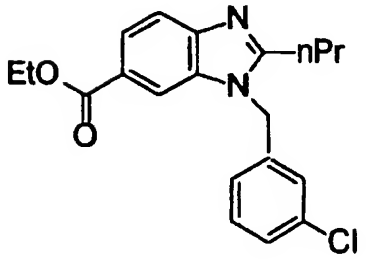
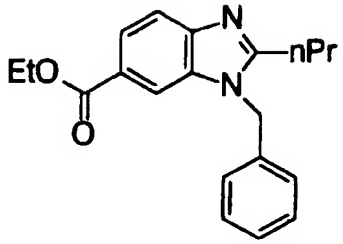


(95)

FIG. 10



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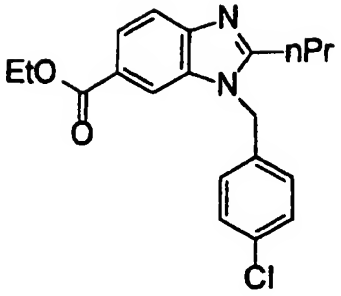

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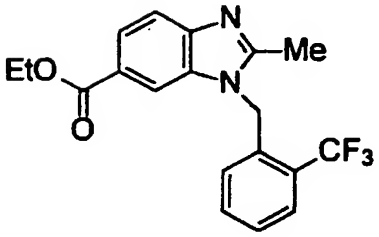

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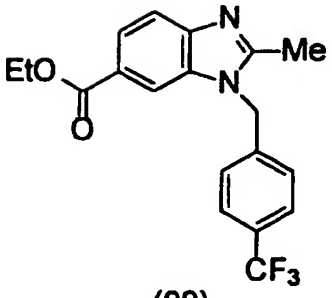

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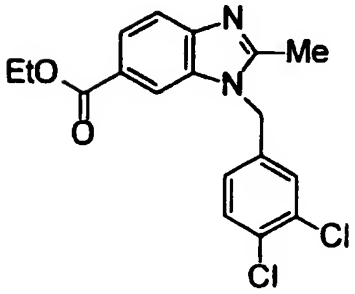

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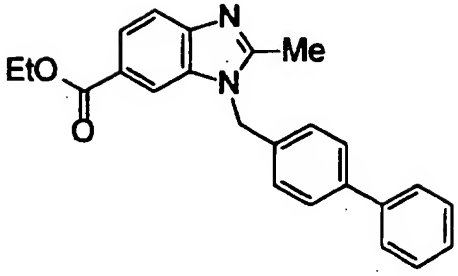
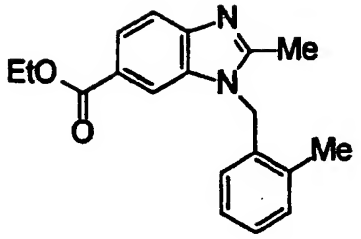


(101)

FIG. 11



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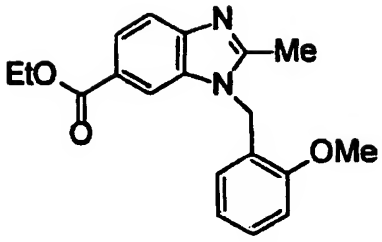

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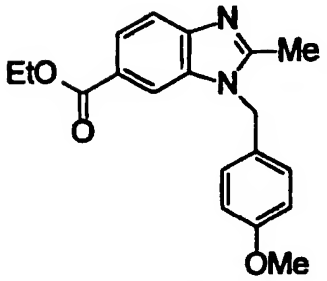
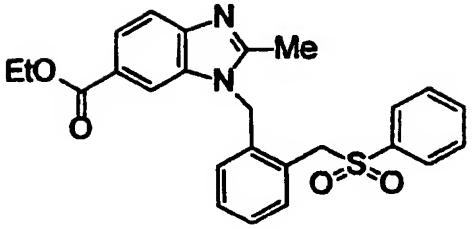


(104)



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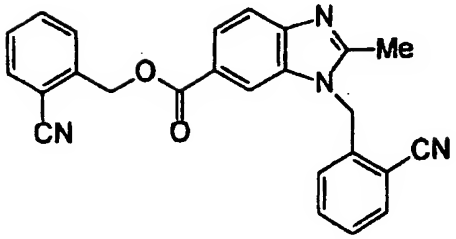

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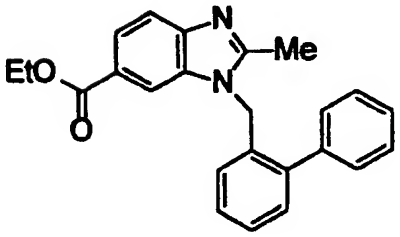
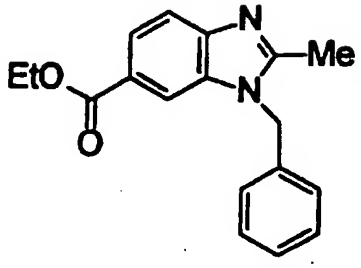


(107)

FIG. 12



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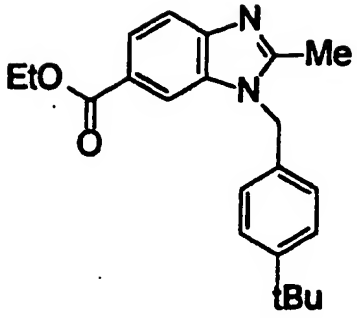

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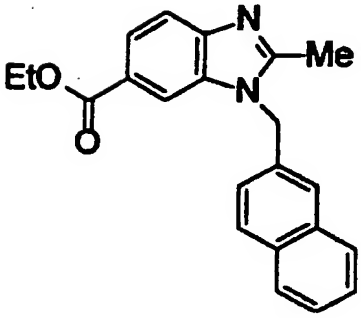

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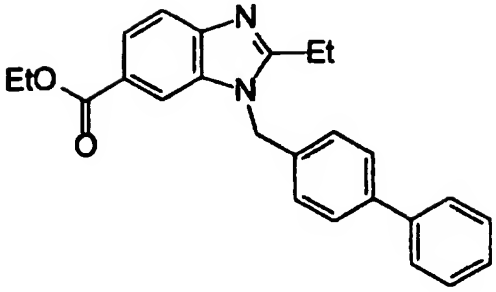

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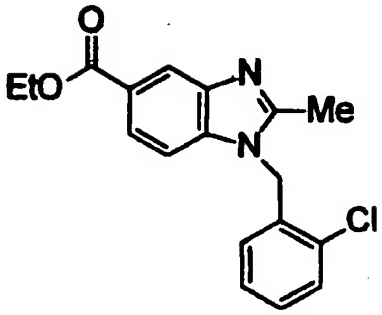
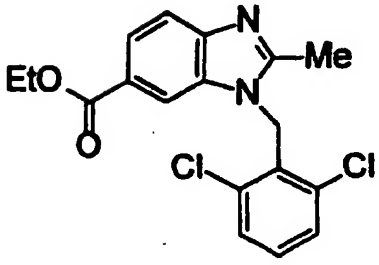
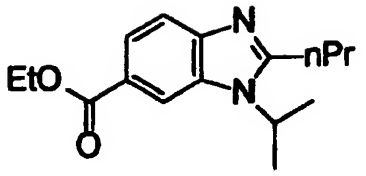


(112)

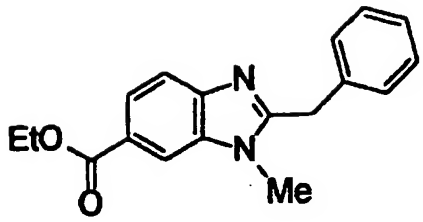


(113)

FIG. 13



(114)



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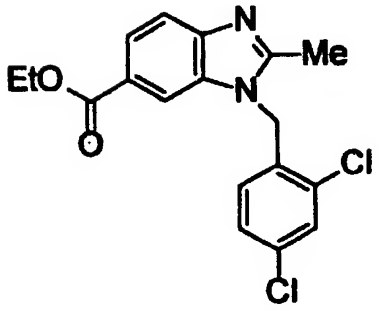

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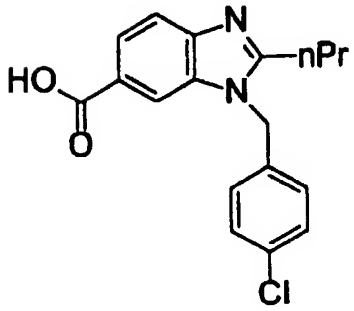

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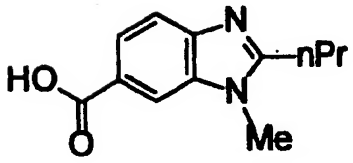
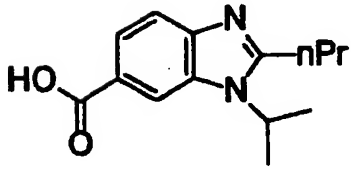
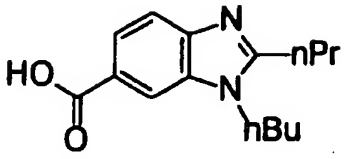


(118)



(119)

FIG. 14



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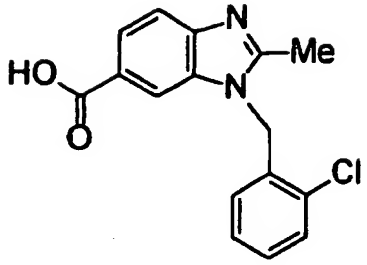

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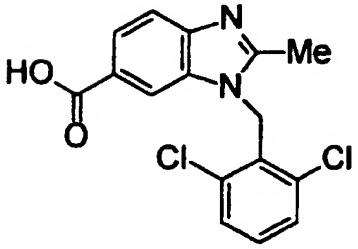

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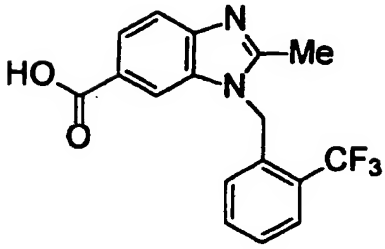
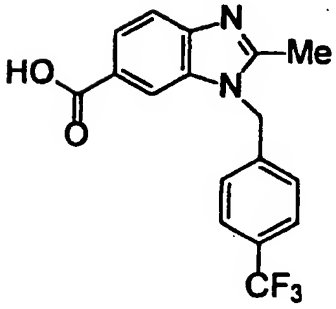
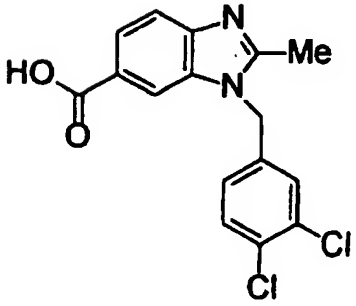


(123)

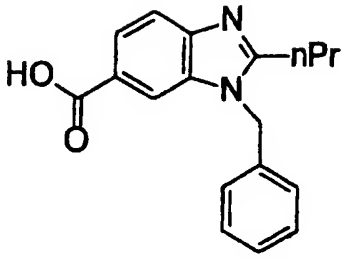


(124)

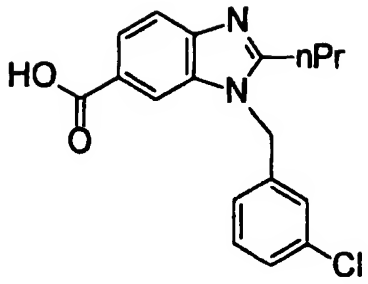


(125)

FIG. 15



(126)



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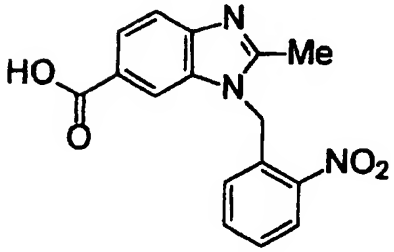

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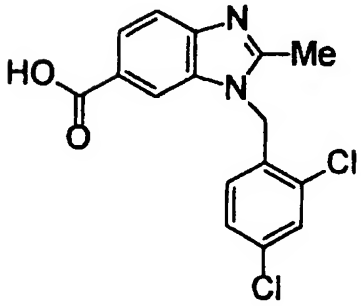

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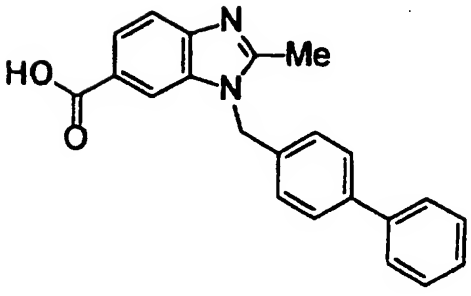

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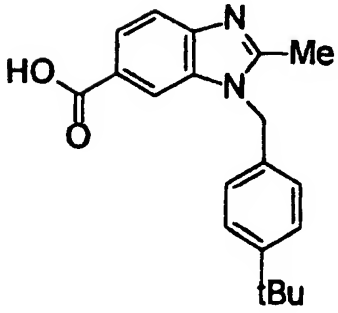
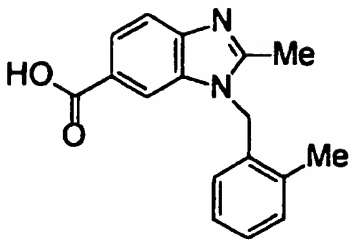


(131)

FIG. 16



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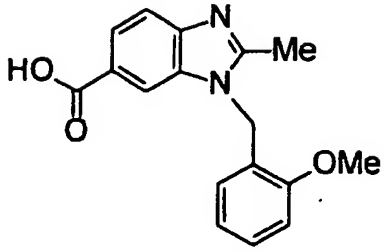

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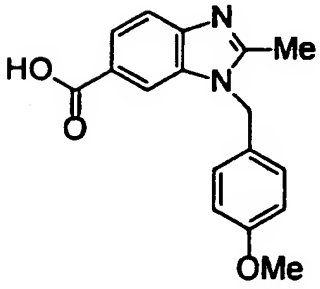

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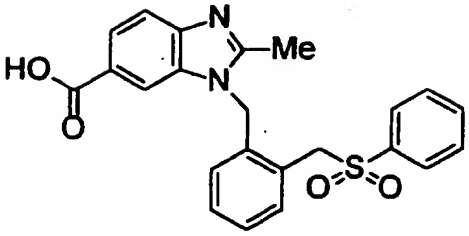

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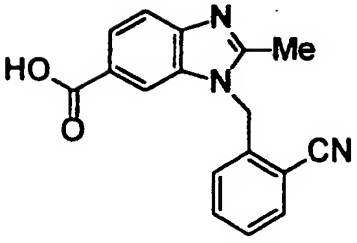
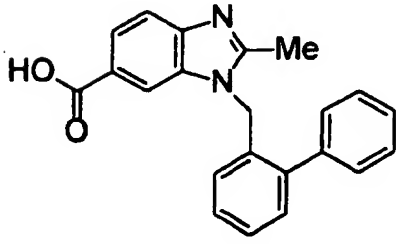
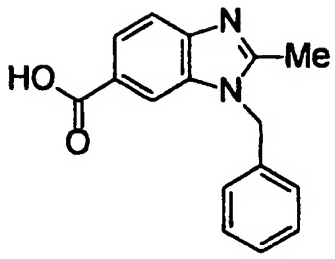


(136)

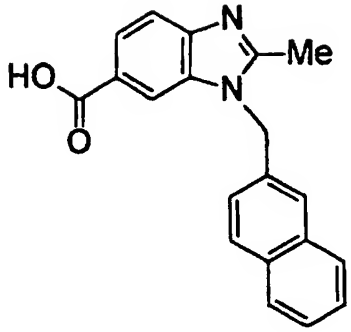


(137)

FIG. 17



(138)



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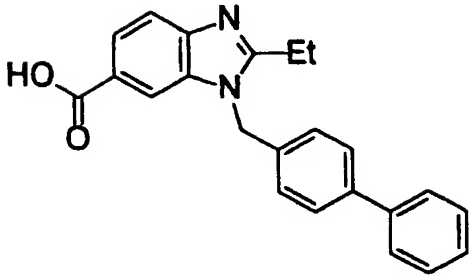

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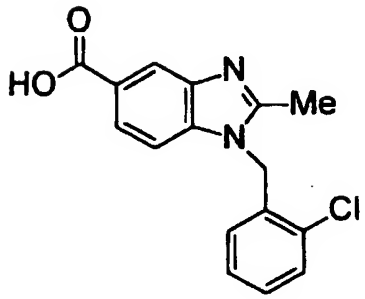

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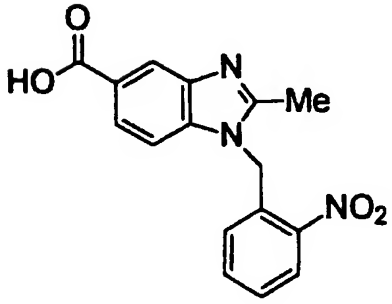

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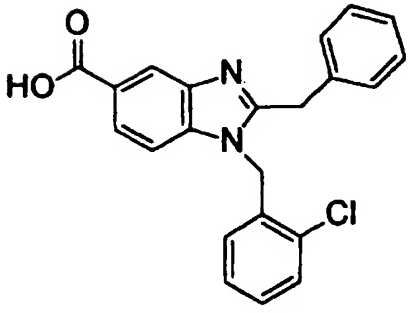
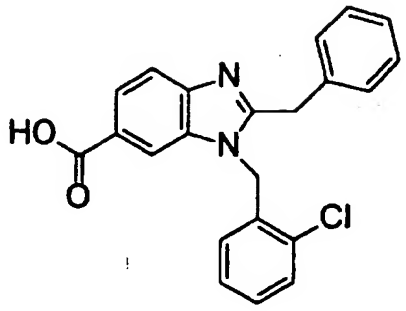
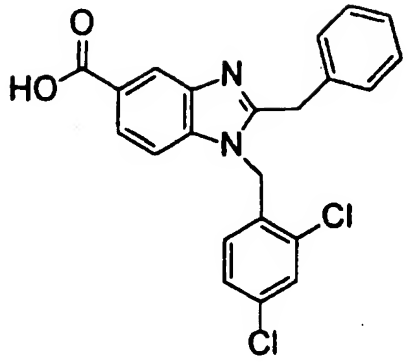


(143)

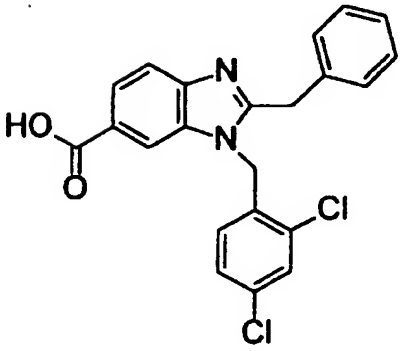
FIG. 18



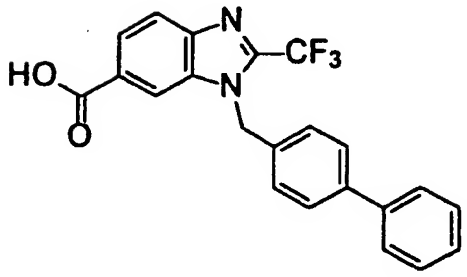
(144)



(145)



(146)



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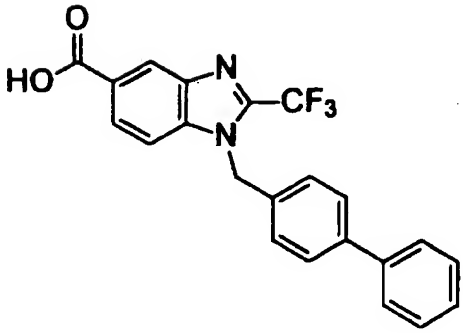
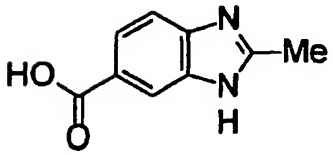
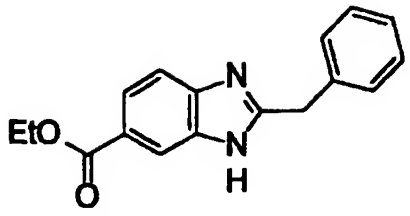


(148)

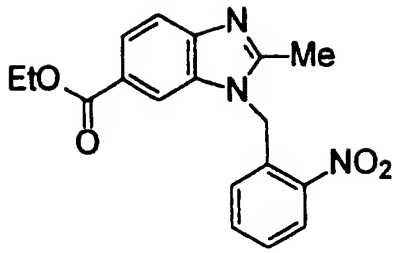


(149)

FIG. 19



(150)



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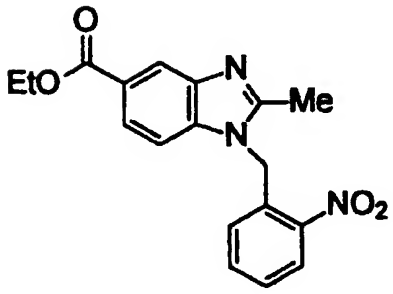
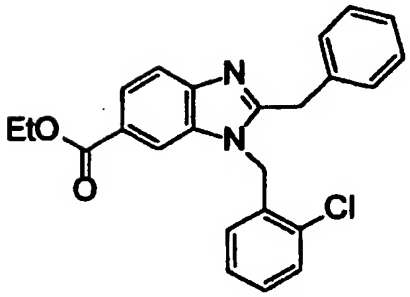
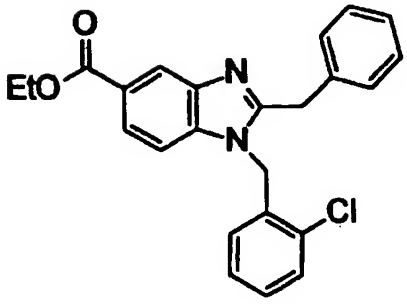


(152)



(153)



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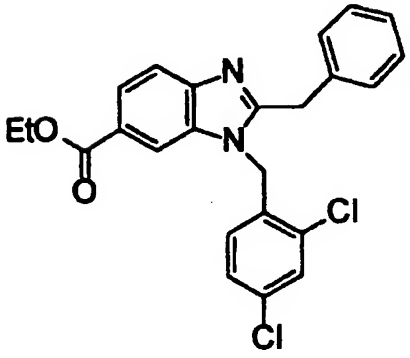
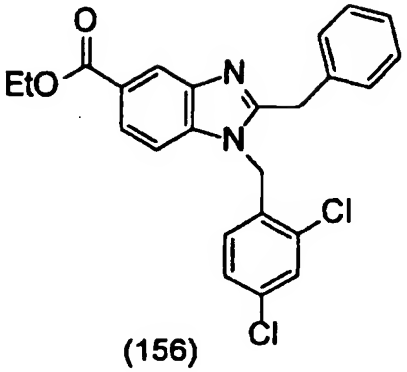
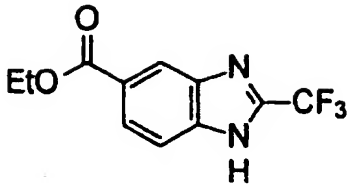


(155)

FIG. 20



(156)



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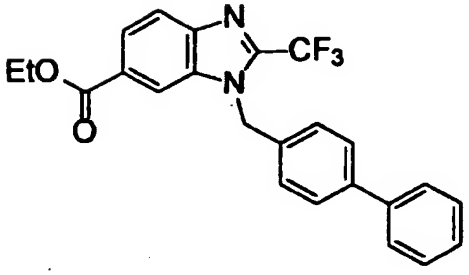
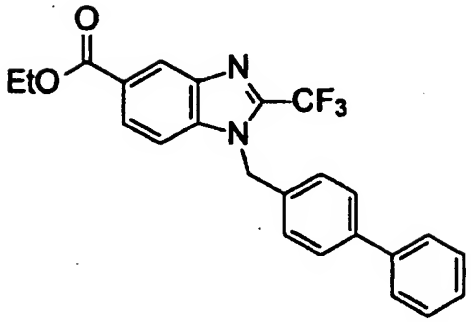


(158)



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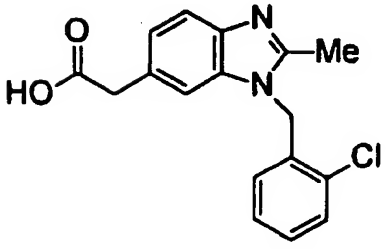

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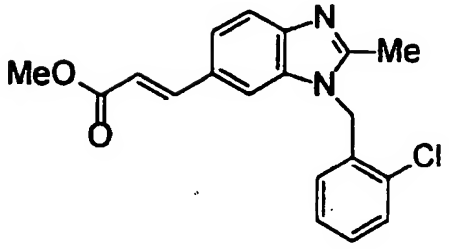
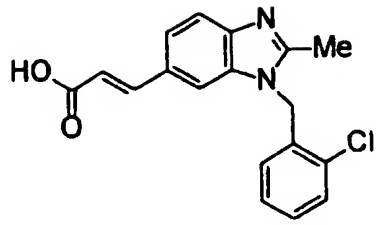
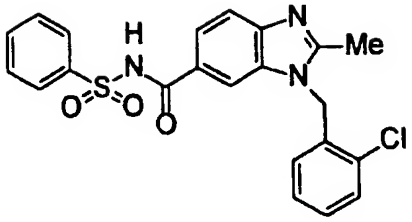


(161)

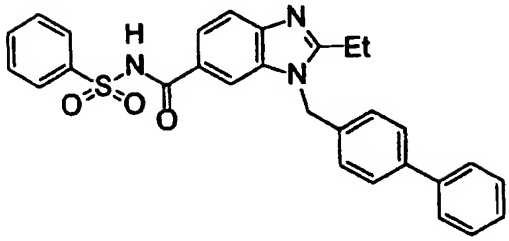
FIG. 21



(162)



(163)



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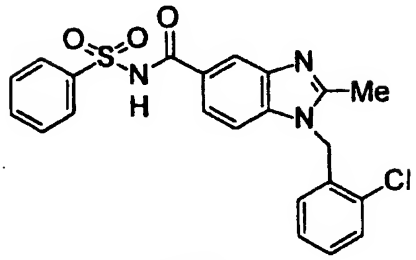

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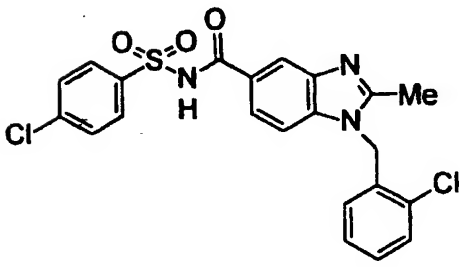

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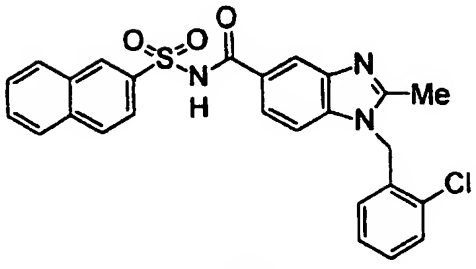
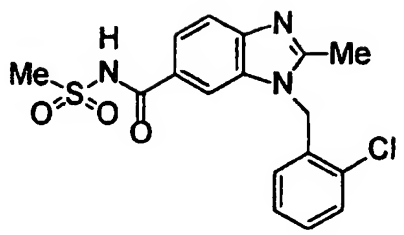


(167)

FIG. 22



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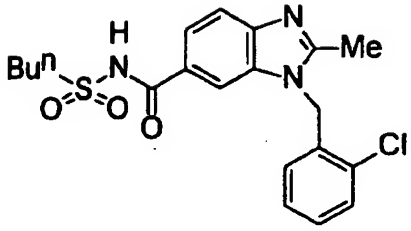

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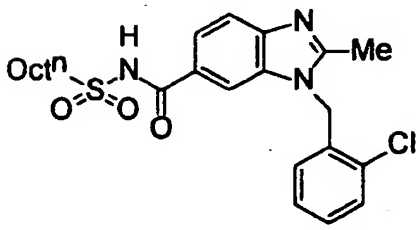

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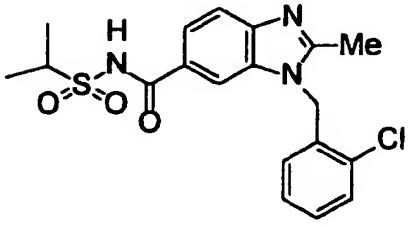

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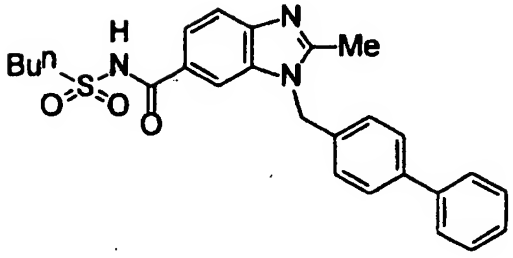

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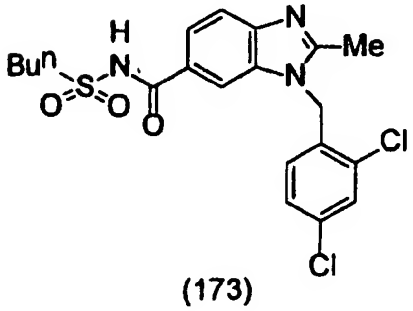
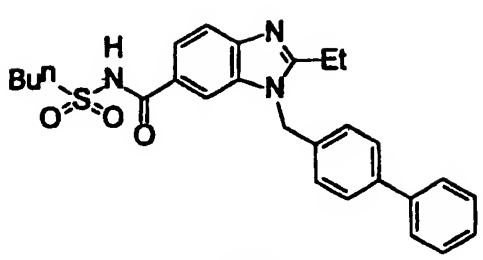
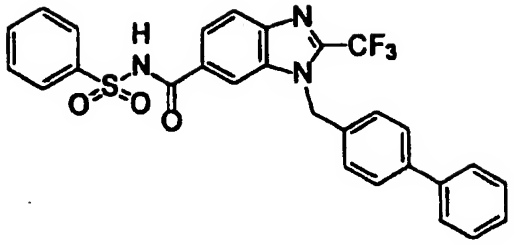


(173)

FIG. 23



(174)



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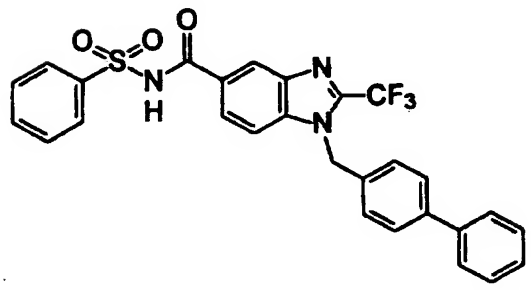
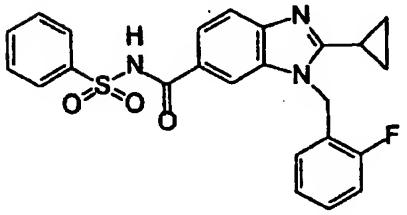
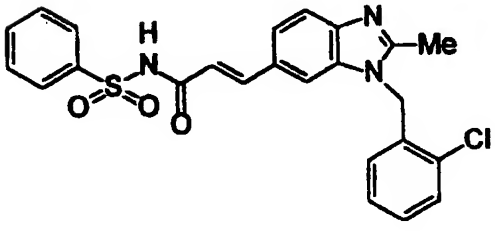


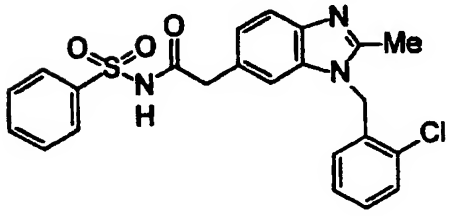
(176)



(177)

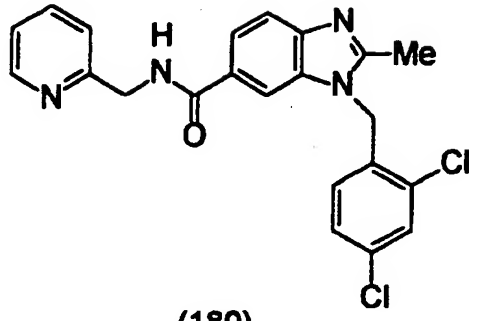


(178)



(179)

FIG. 24



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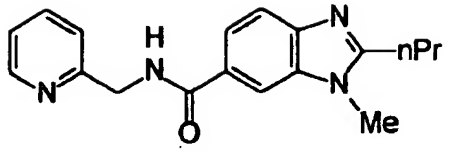

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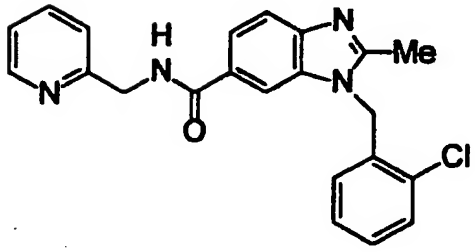

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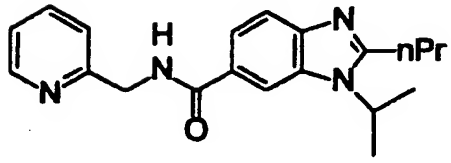

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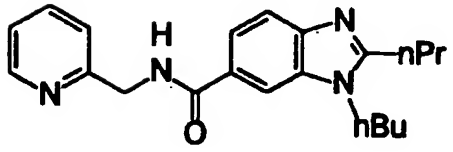

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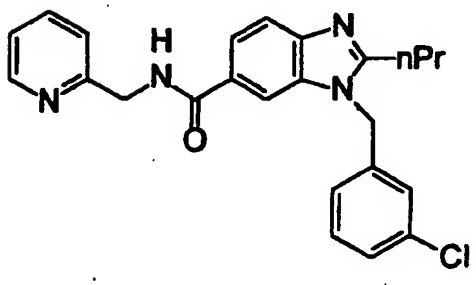
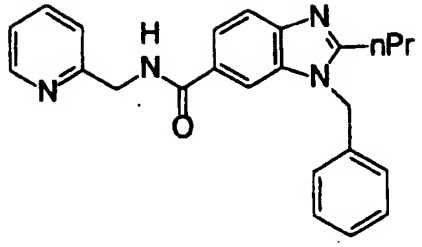
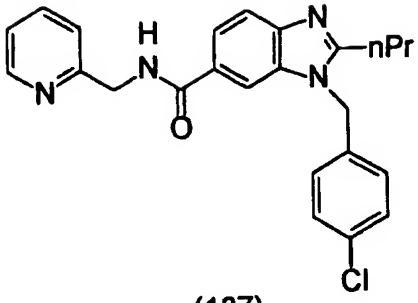


(185)

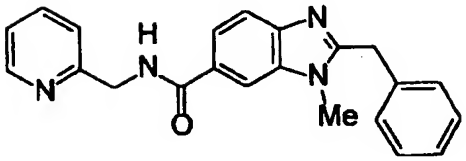
FIG. 25



(186)



(187)



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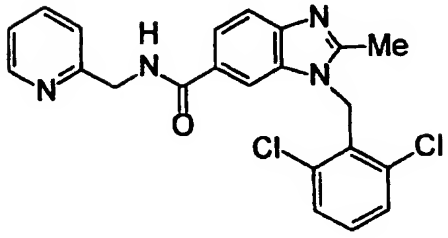

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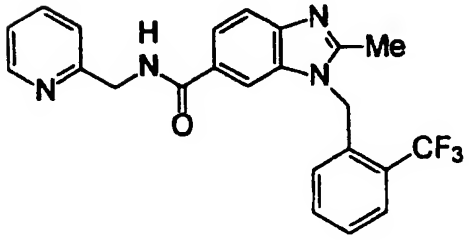
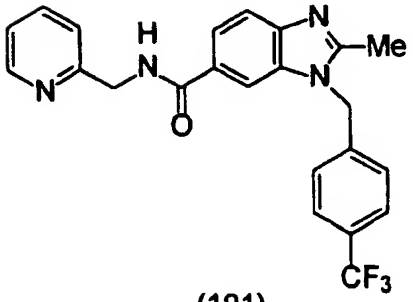
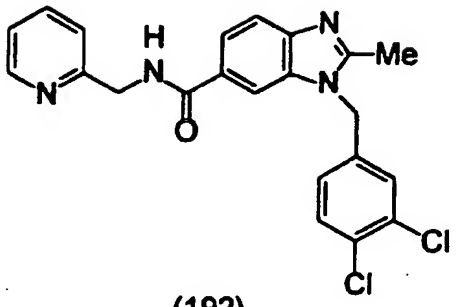


(190)

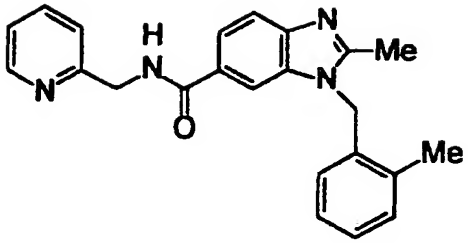


(191)

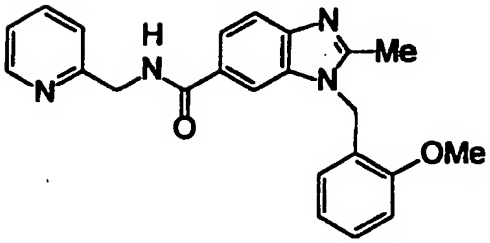
FIG. 26



(192)



(193)



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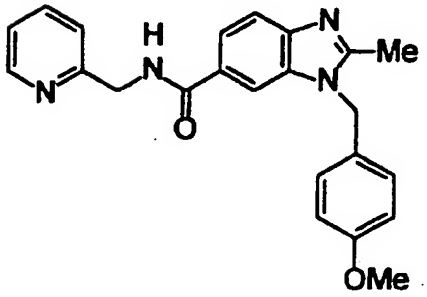

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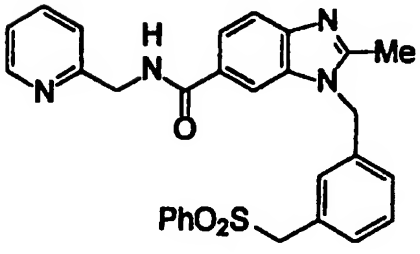
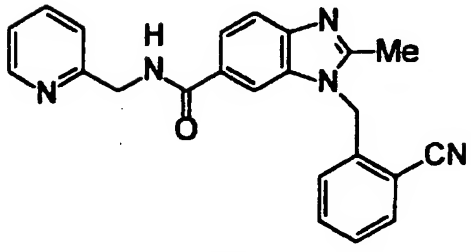
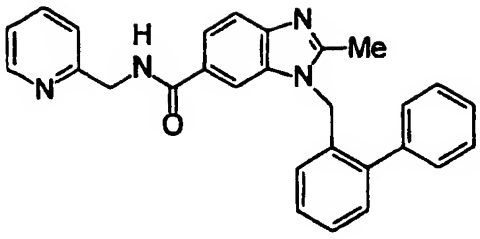


(196)

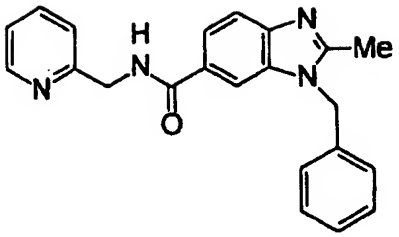


(197)

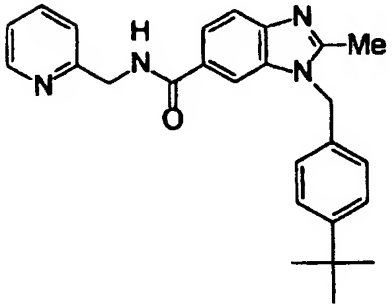
FIG. 27



(198)



(199)



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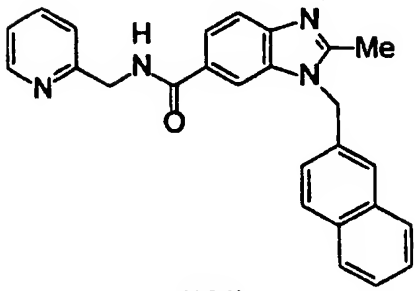

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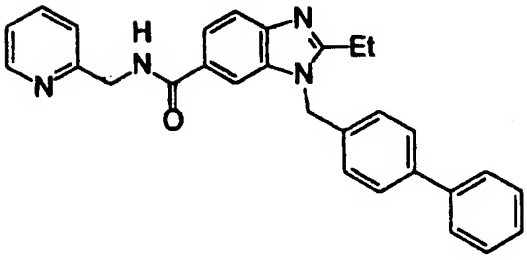
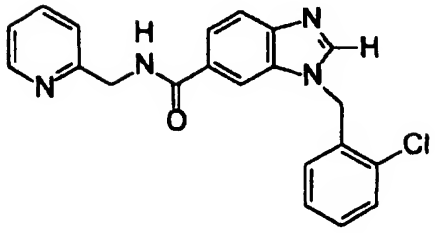
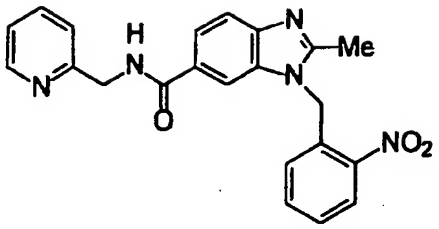


(202)



(203)

FIG. 28



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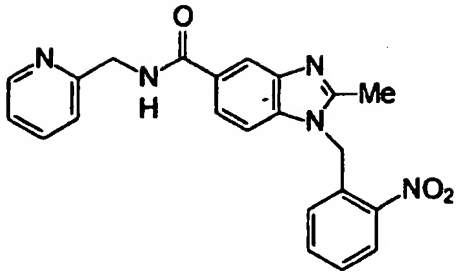

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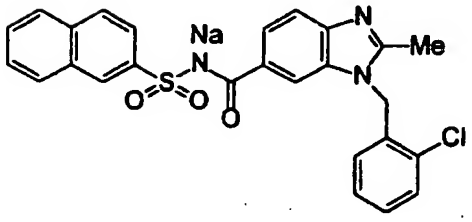

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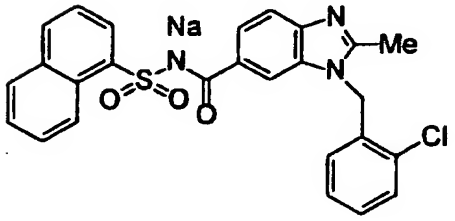

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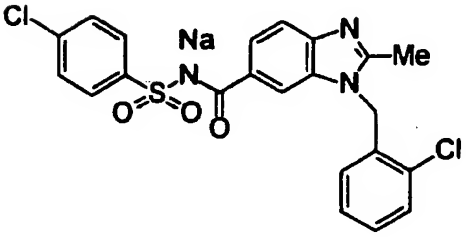

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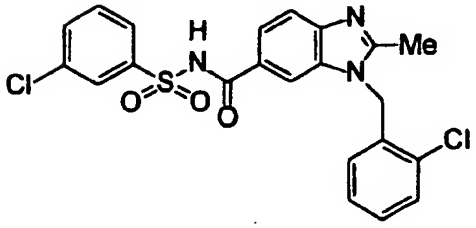
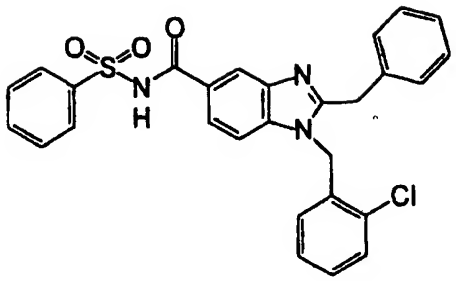


(209)

FIG. 29



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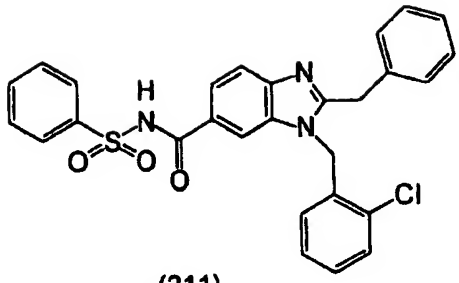

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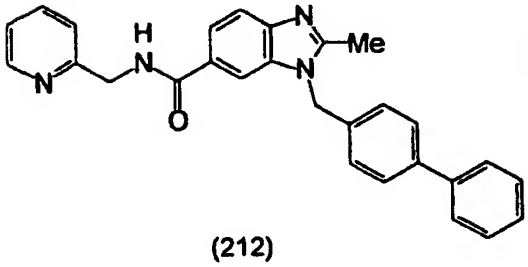
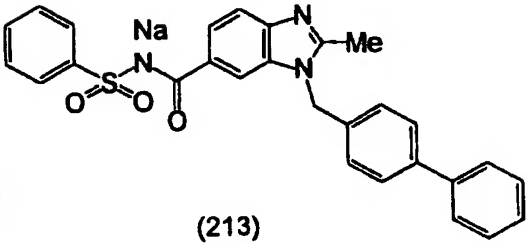


(212)



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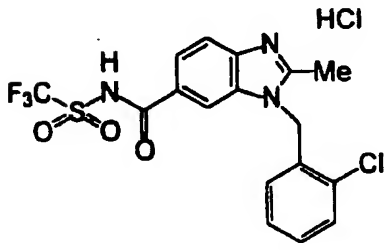

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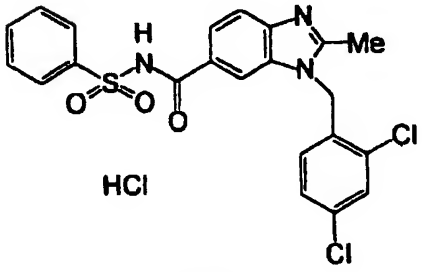

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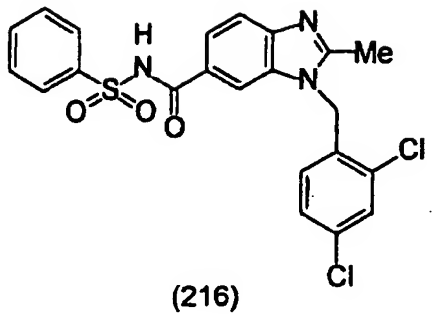
FIG. 30



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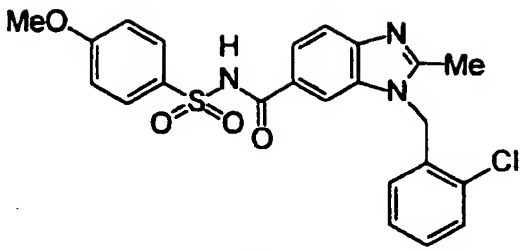

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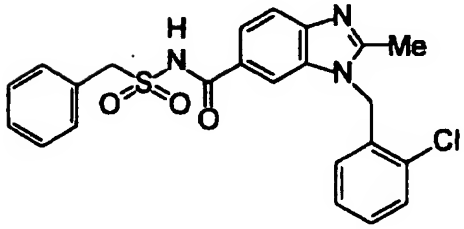

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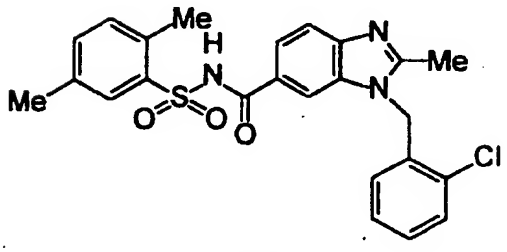

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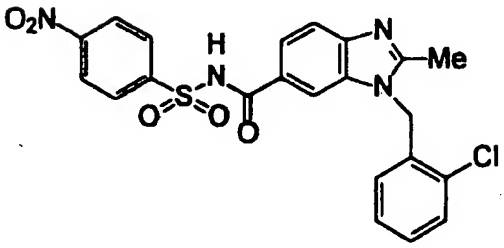

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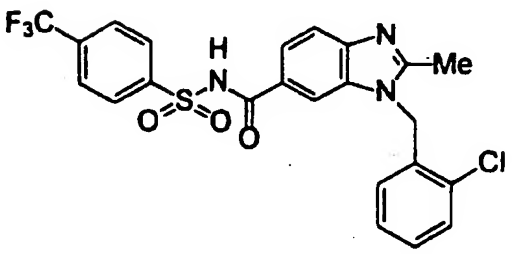

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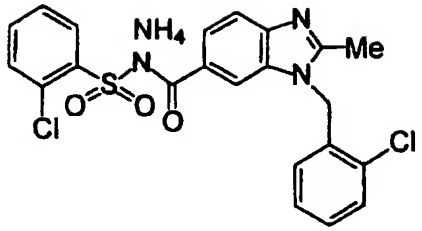
FIG. 31



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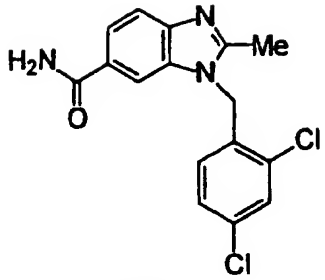

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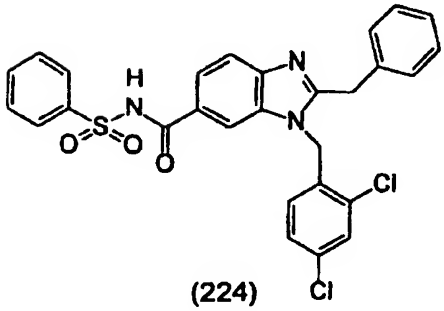

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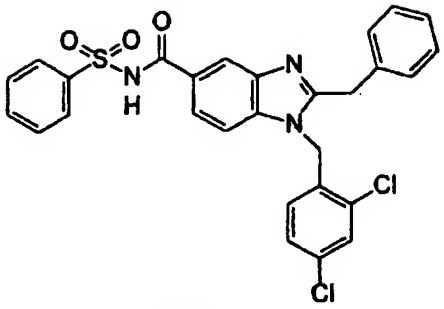

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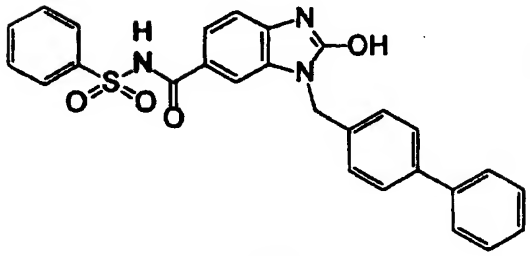

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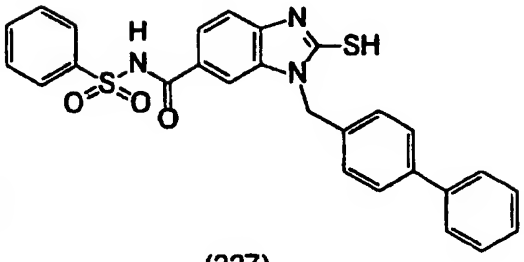

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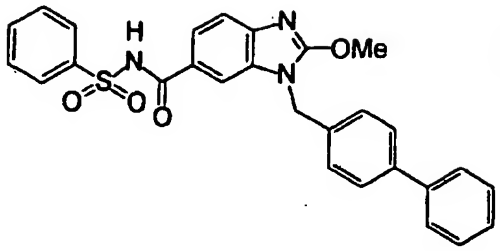
FIG. 32



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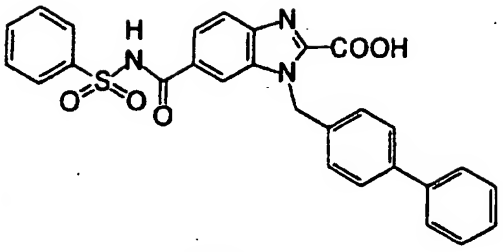

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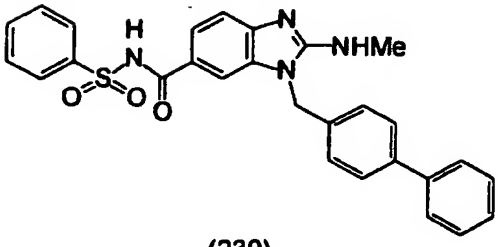

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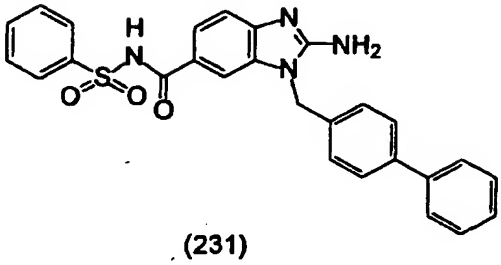

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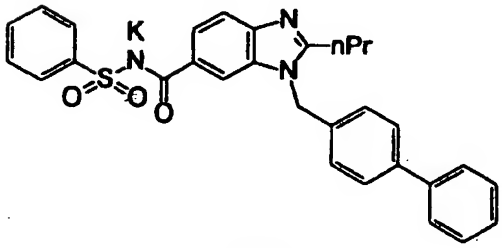

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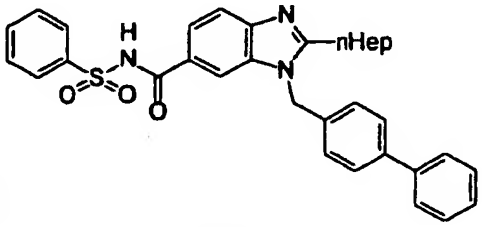
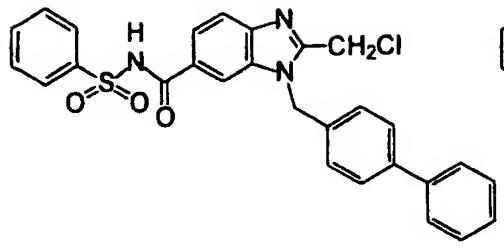


(233)

FIG. 33



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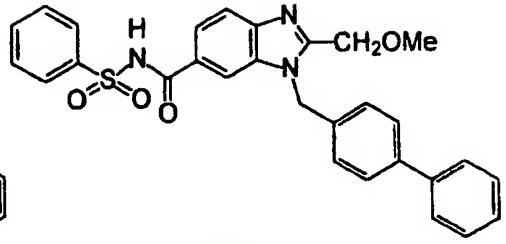

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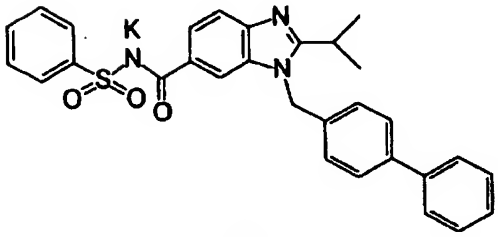

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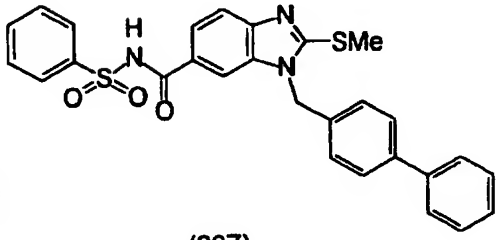

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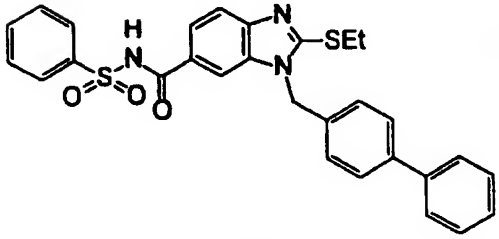

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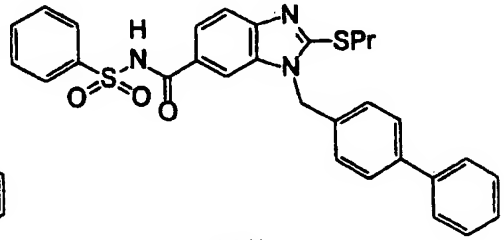
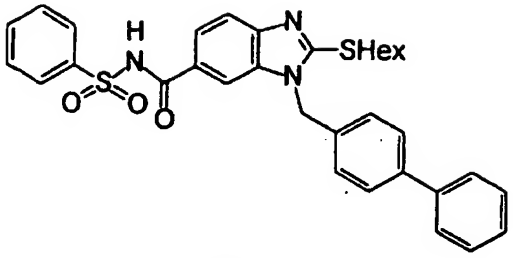


(239)

FIG. 34



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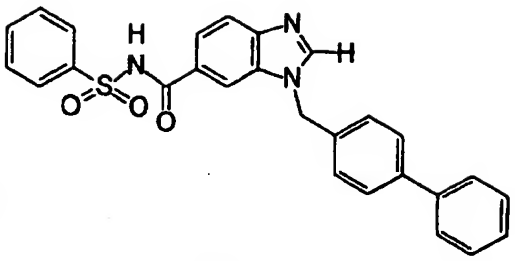

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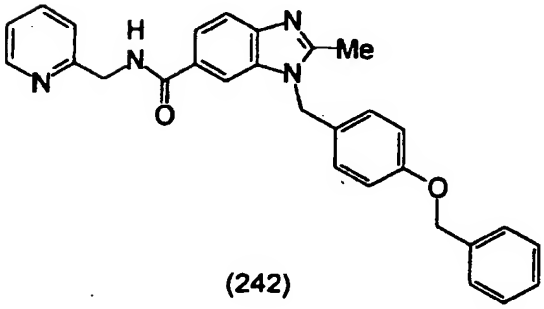

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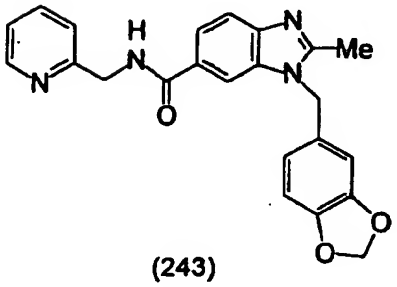

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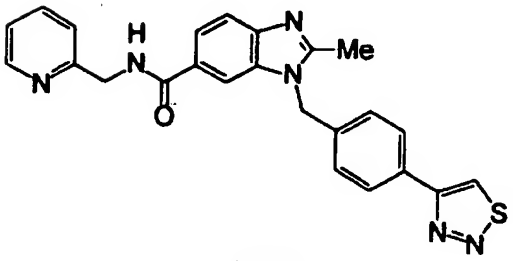

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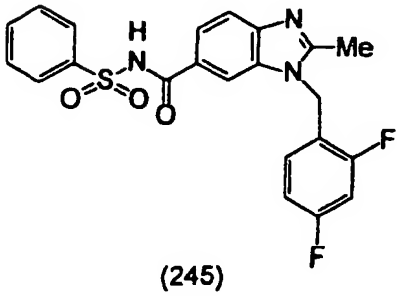
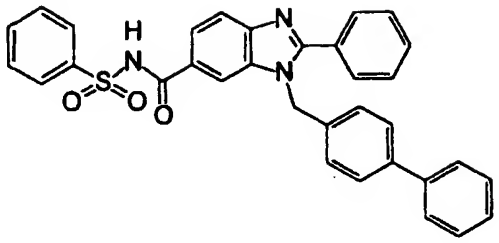


(245)

FIG. 35



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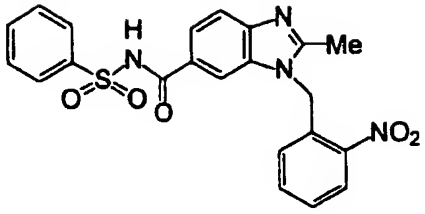

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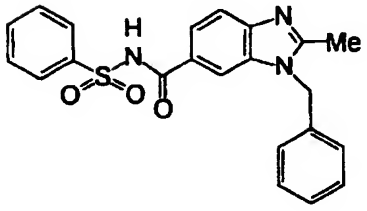

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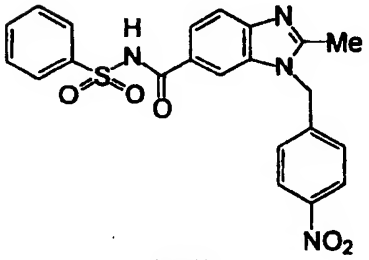

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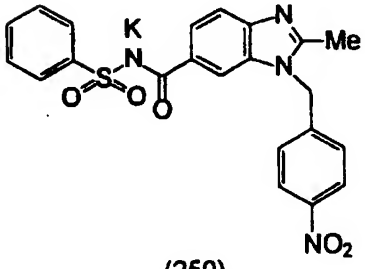

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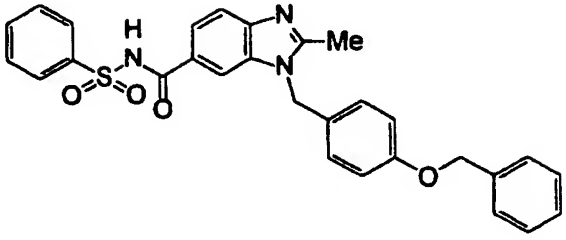

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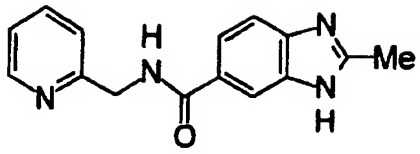
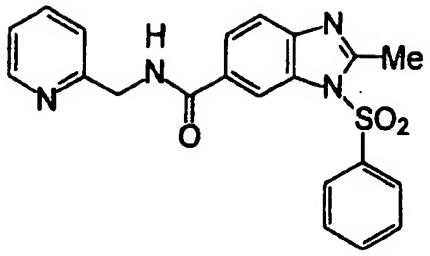
FIG. 36



(252)



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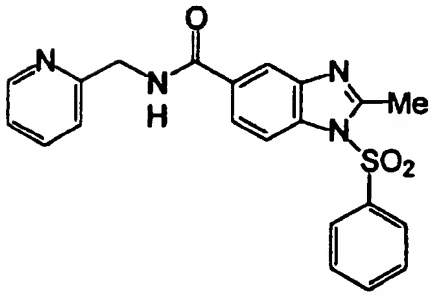

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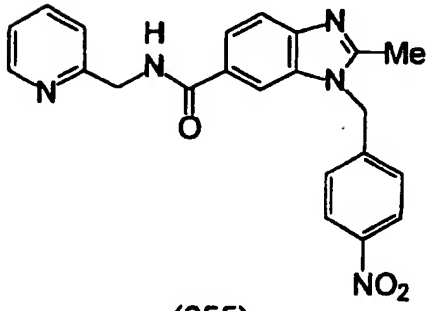

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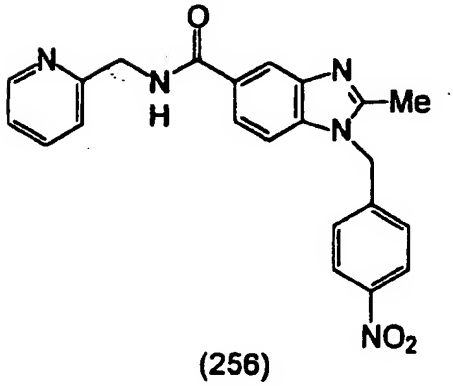
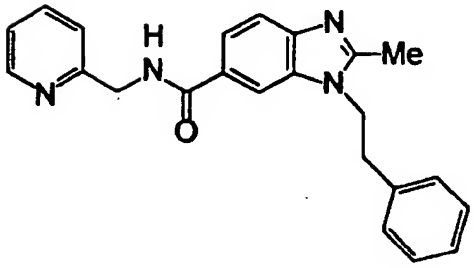
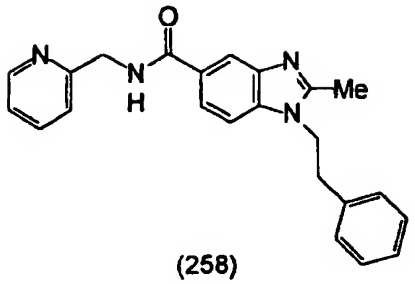


(256)

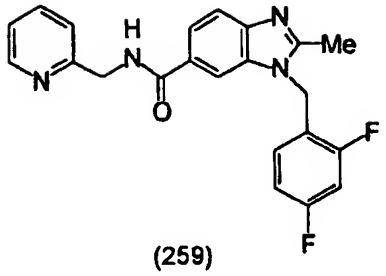


(257)

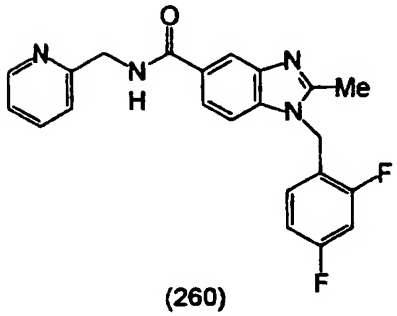
FIG. 37



(258)



(259)



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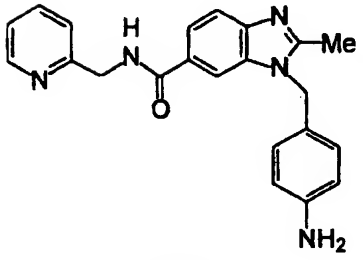

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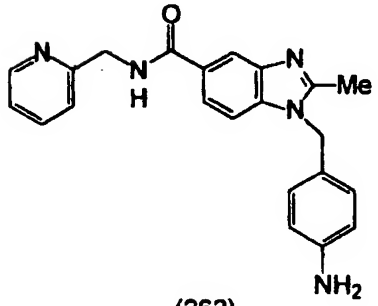

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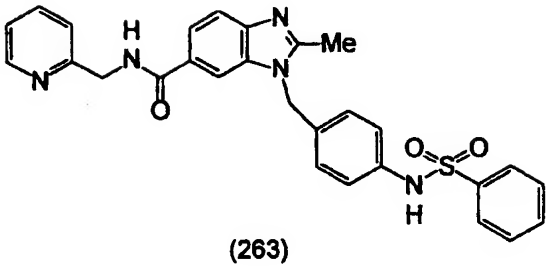
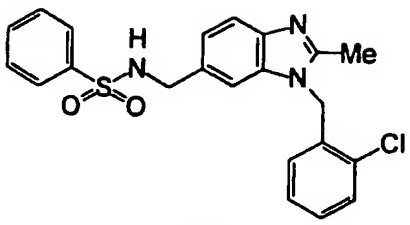


(263)

FIG. 38



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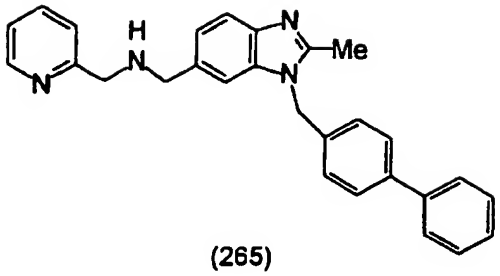

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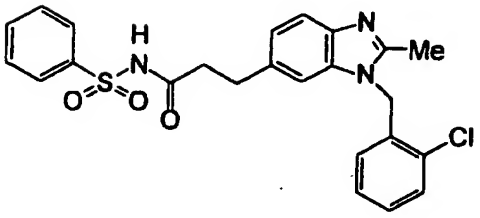
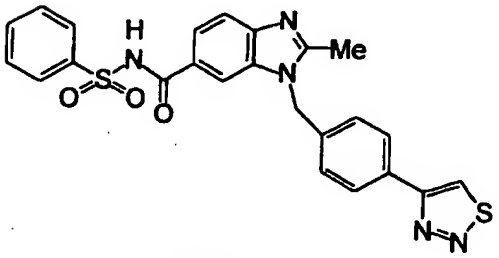


(266)



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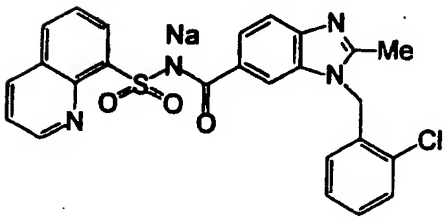

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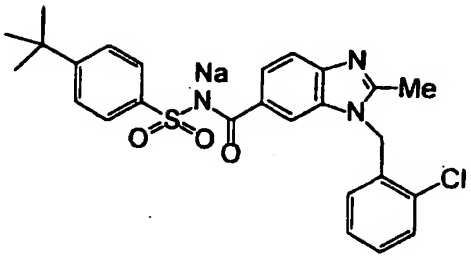
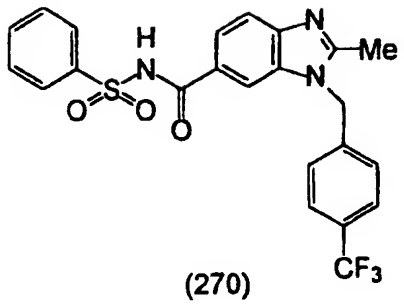


(269)

FIG. 39



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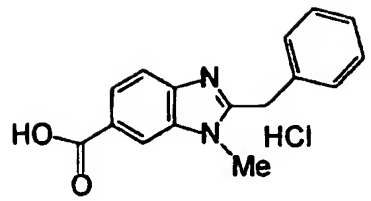

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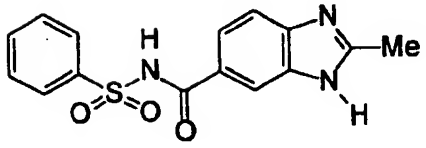

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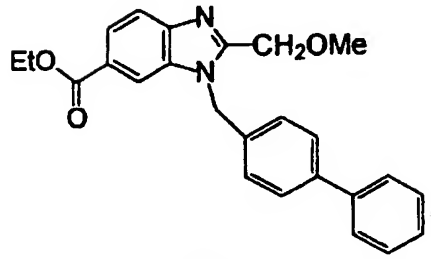

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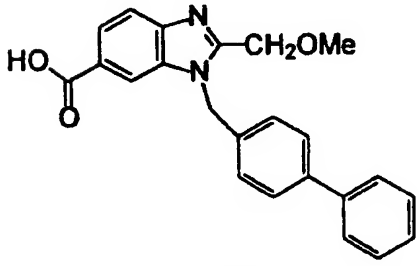

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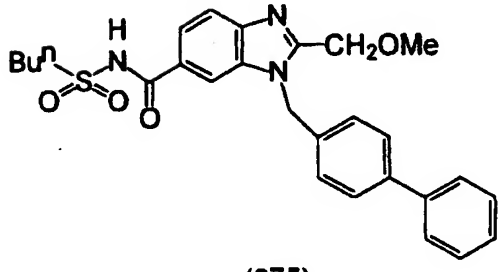
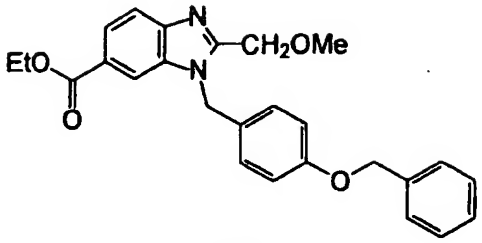


(275)

FIG. 40



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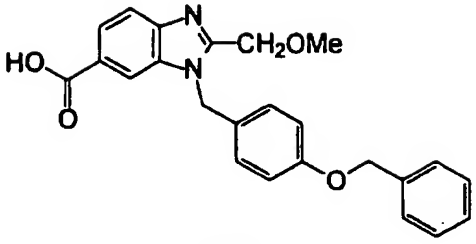

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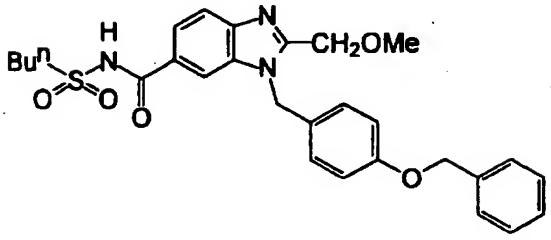

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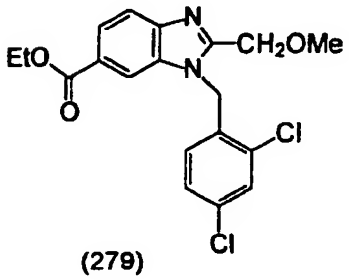

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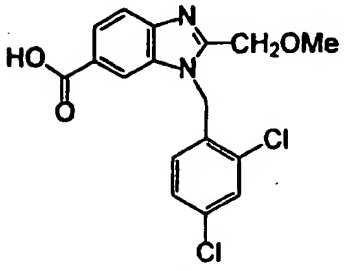

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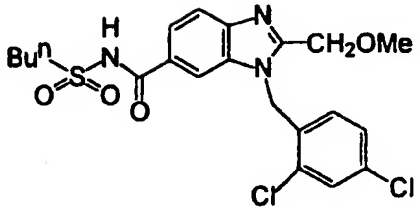
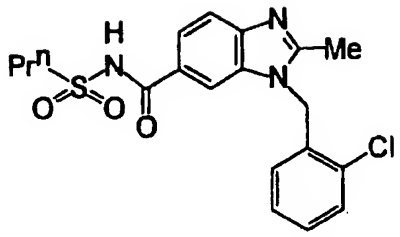


(281)

FIG. 41



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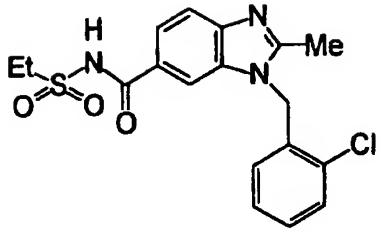

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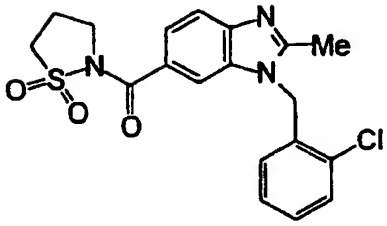

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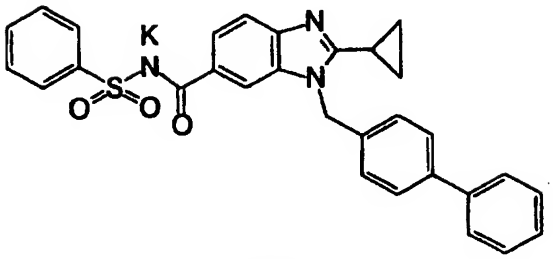

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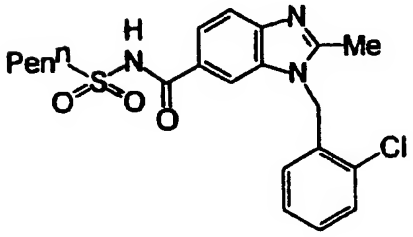

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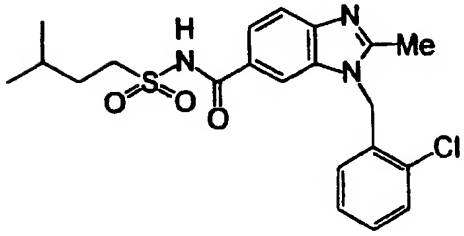
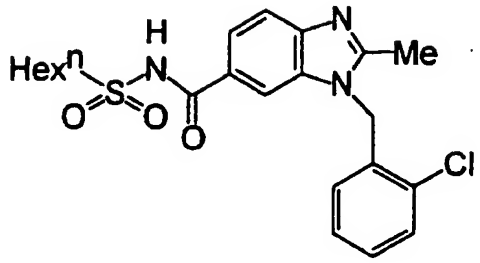


(287)

FIG. 42



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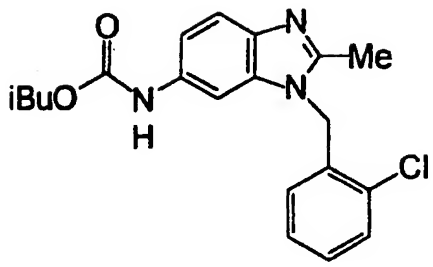

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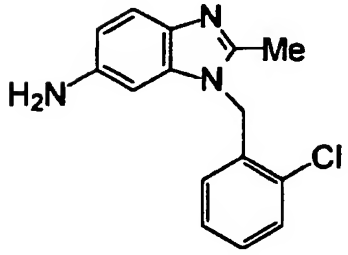

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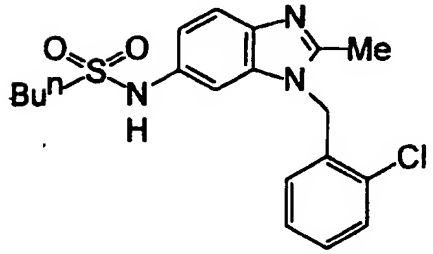

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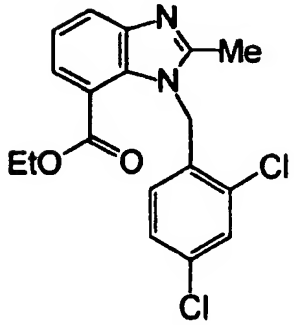

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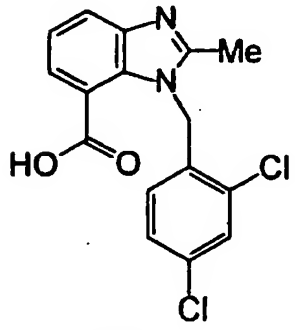
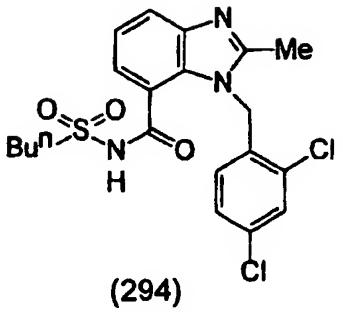


(293)

FIG. 43



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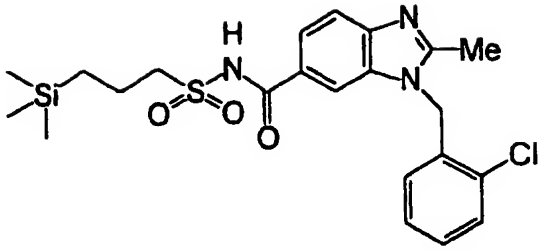

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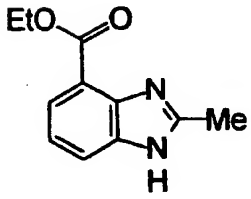

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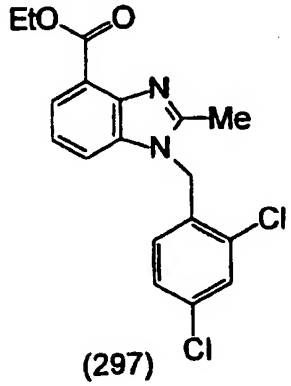

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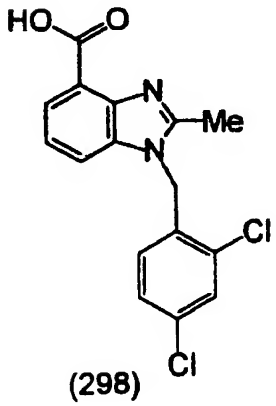

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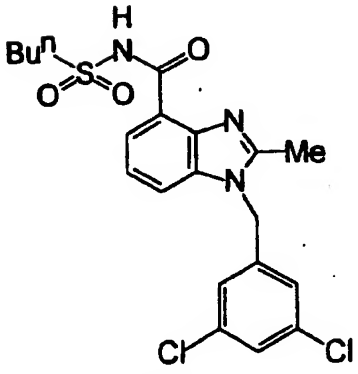
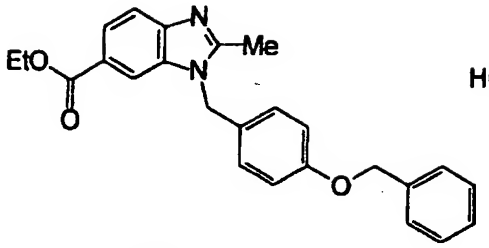


(299)

FIG. 44



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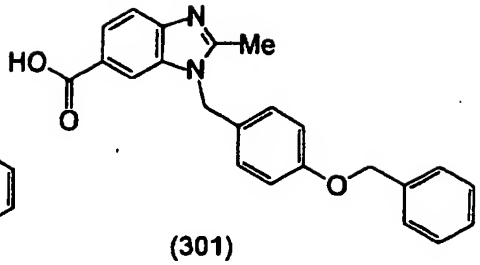

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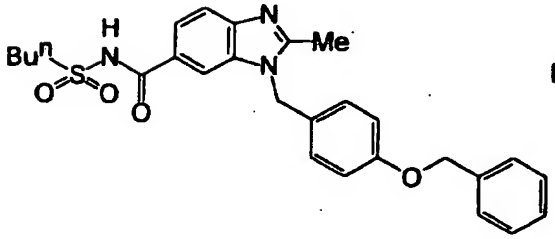

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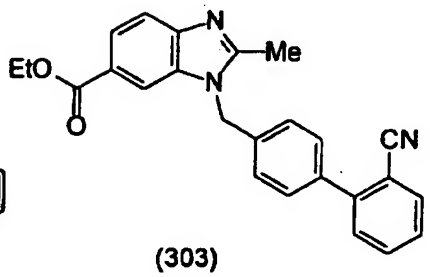

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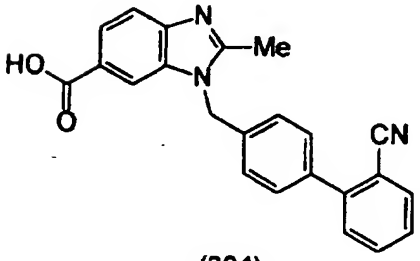

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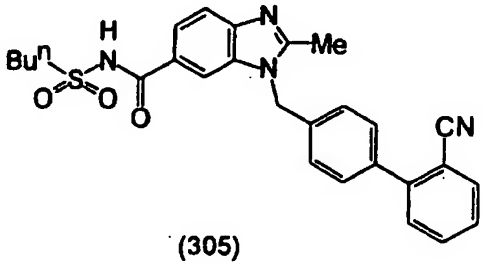
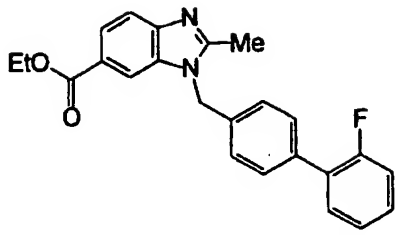
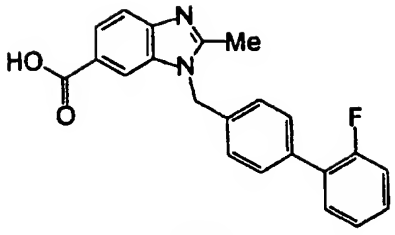


(305)

FIG. 45



(306)



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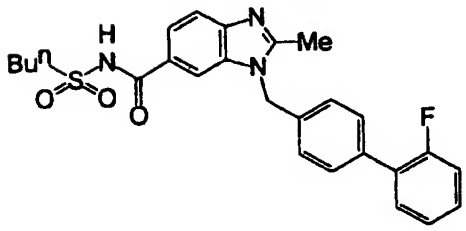

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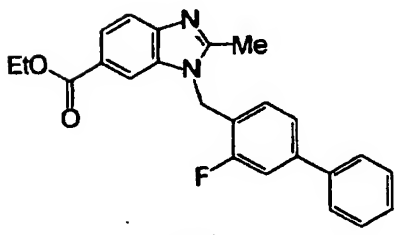

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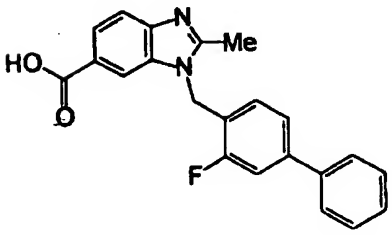
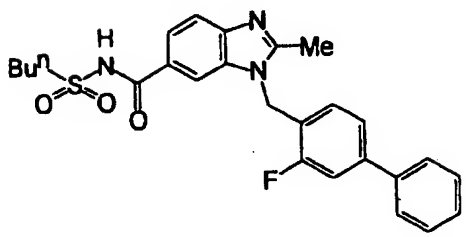
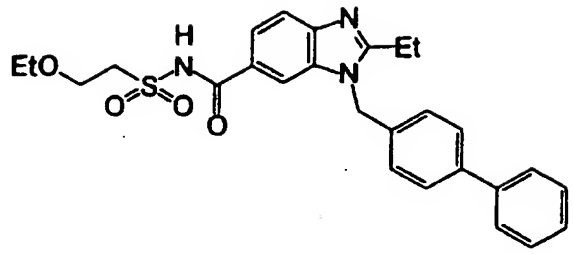


(310)

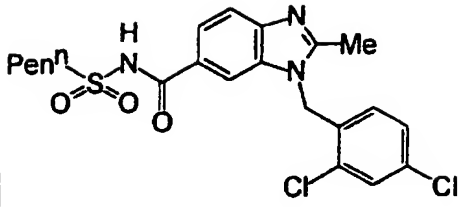


(311)

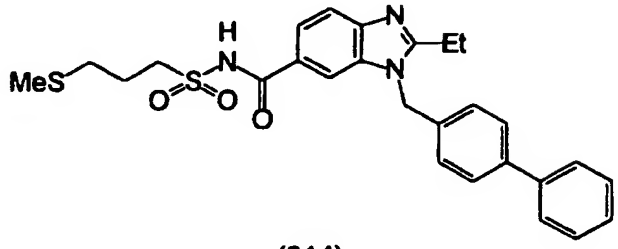
FIG. 46



(312)



(313)



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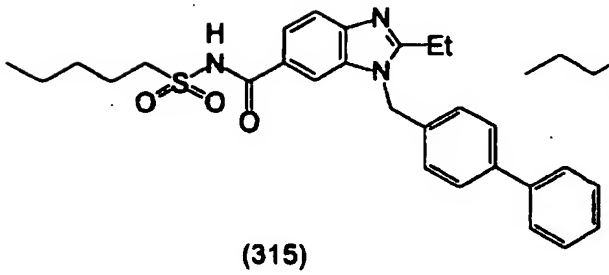

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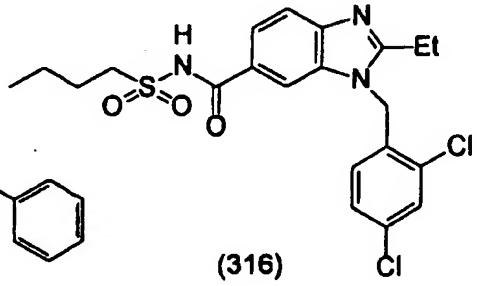
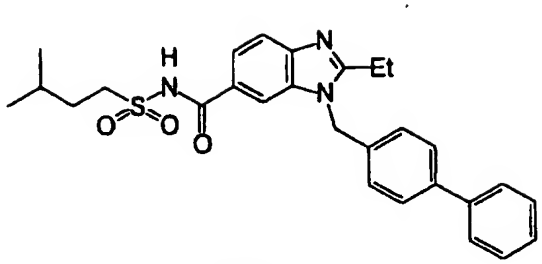


(316)

FIG. 47



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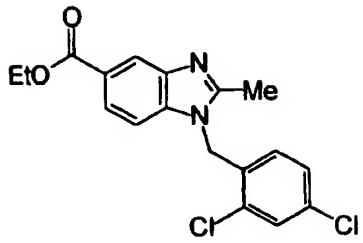
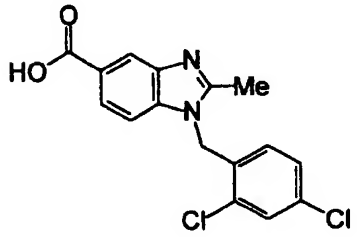


(318)



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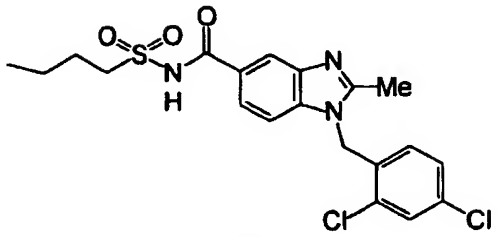

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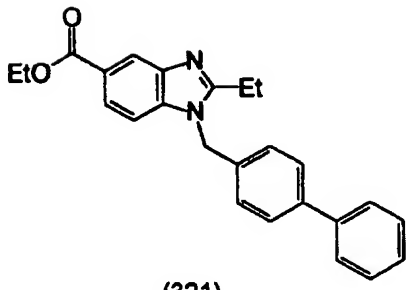

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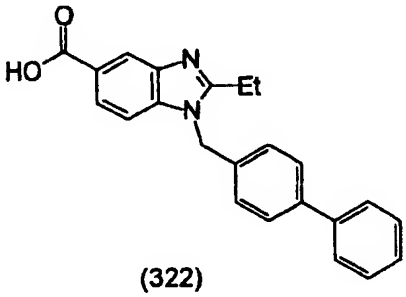
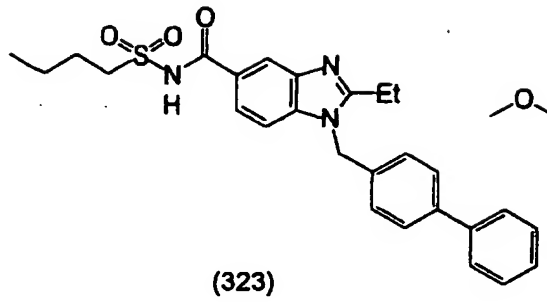


(322)

FIG. 48



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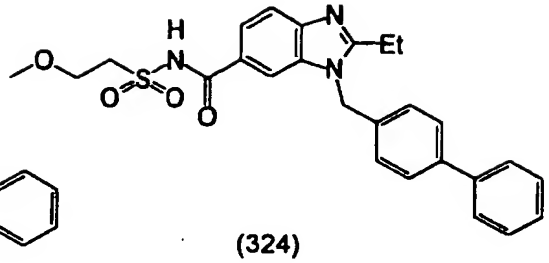

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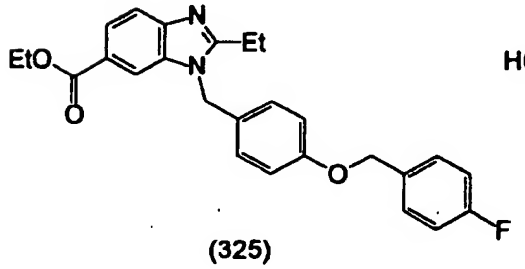

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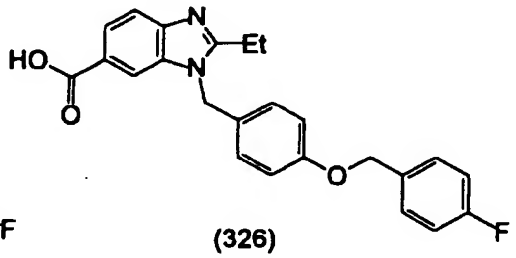

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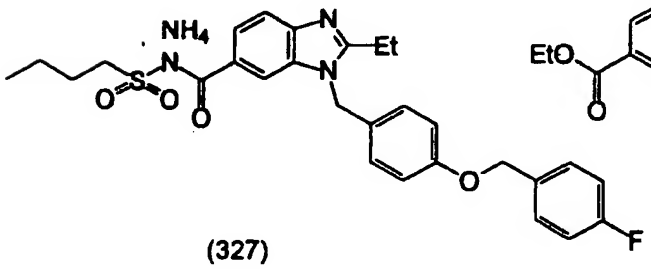

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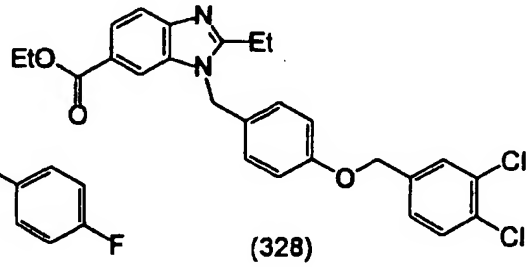
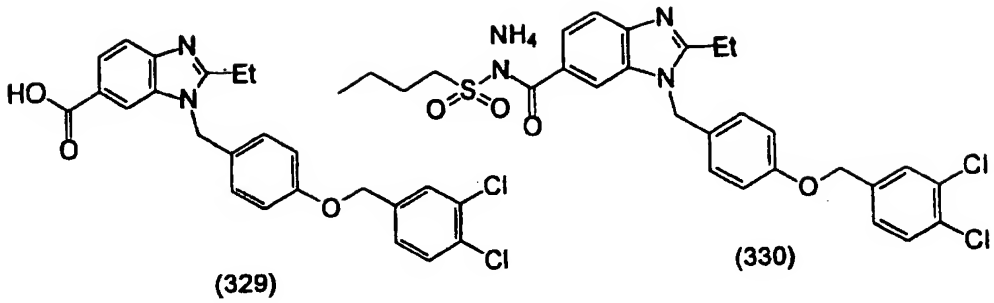
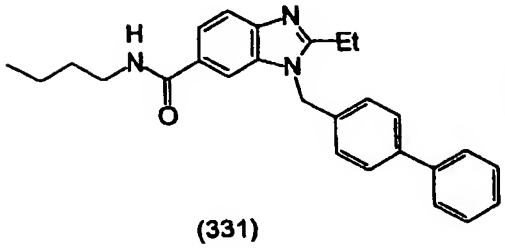


(328)

FIG. 49



(329) (330)



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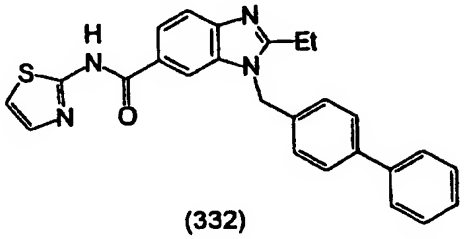

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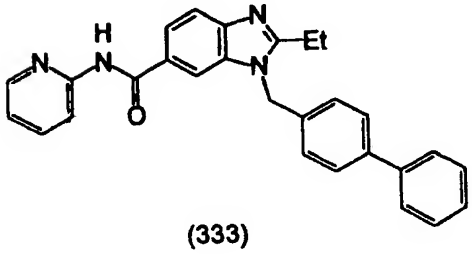

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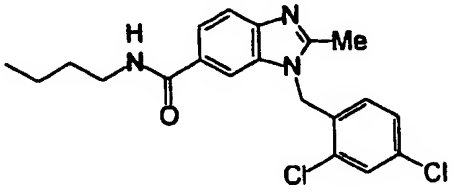
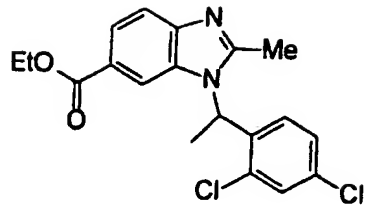


(334)

FIG. 50



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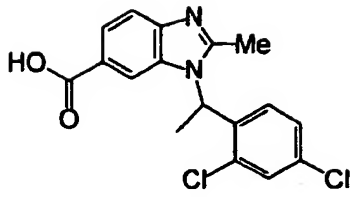

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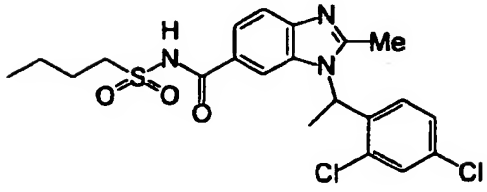

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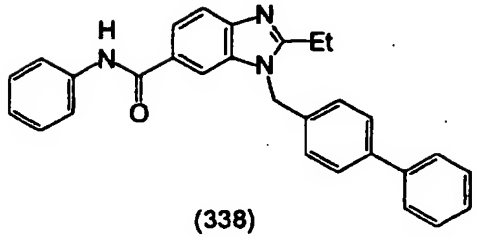

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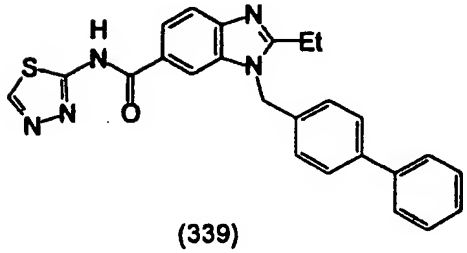

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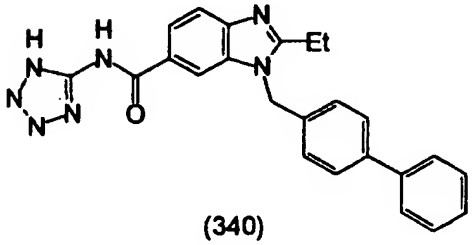
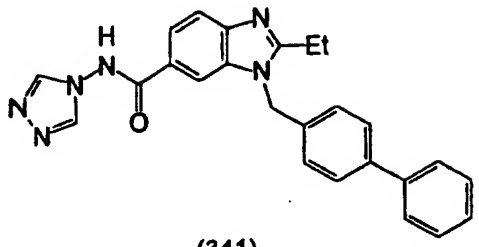


(340)

FIG. 51



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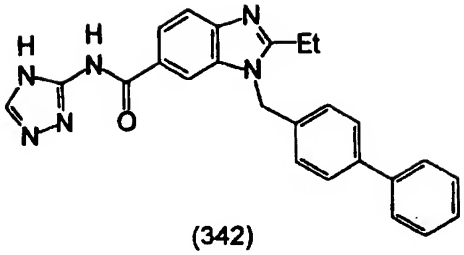

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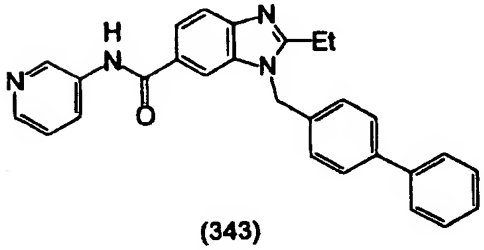

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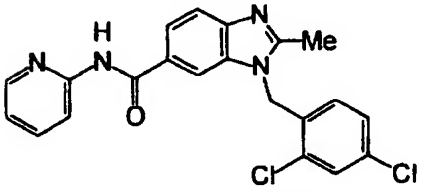

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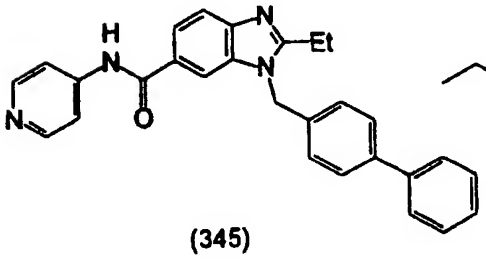

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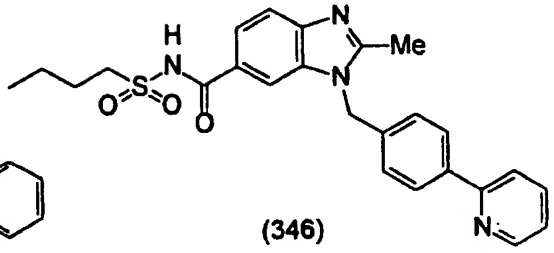

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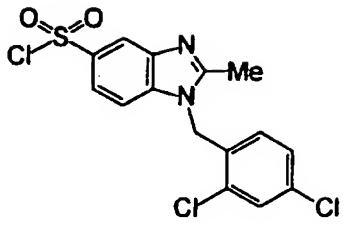
FIG. 52



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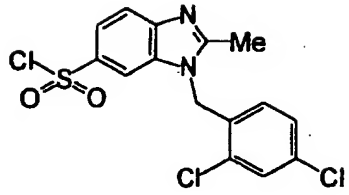

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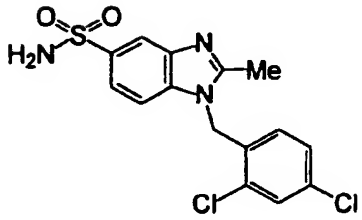

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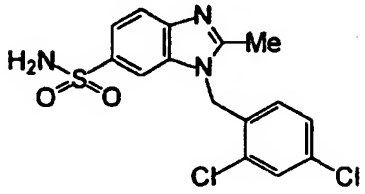

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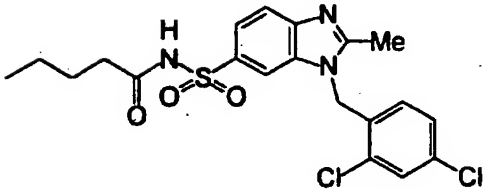

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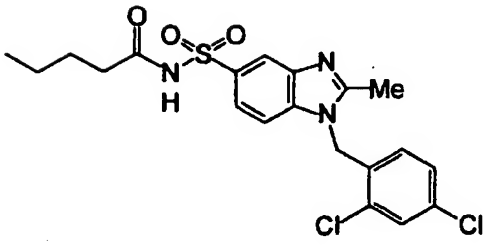

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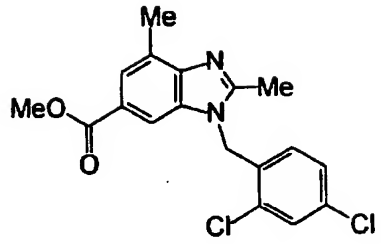
FIG. 53



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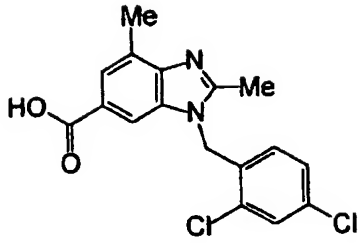

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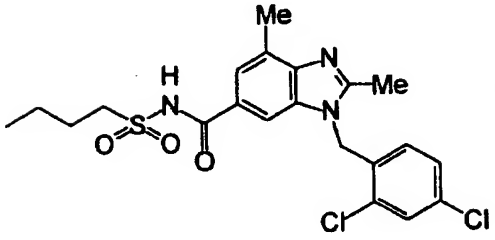

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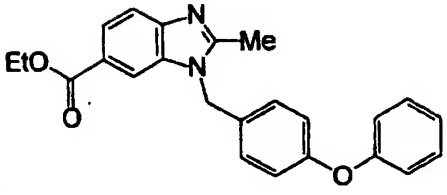

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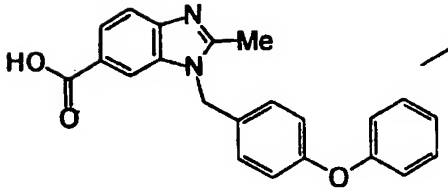

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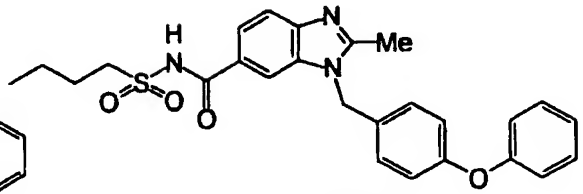
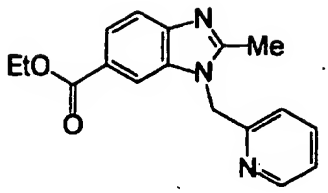


(358)

FIG. 54



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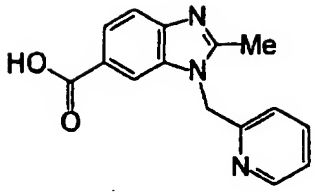

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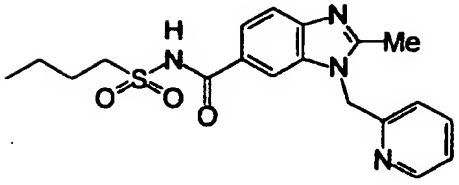

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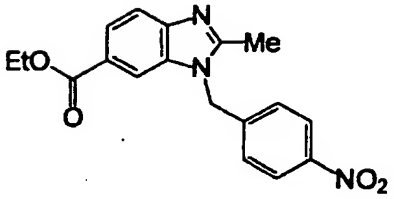

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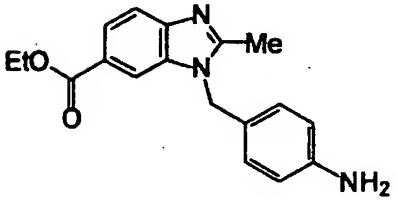

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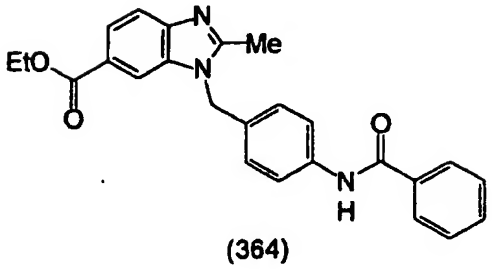
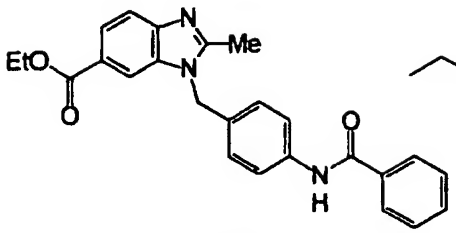


(364)

FIG. 55



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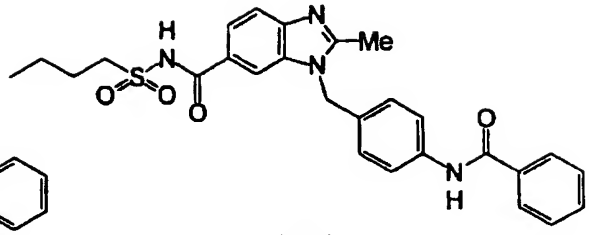

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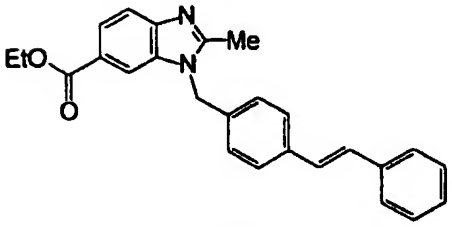

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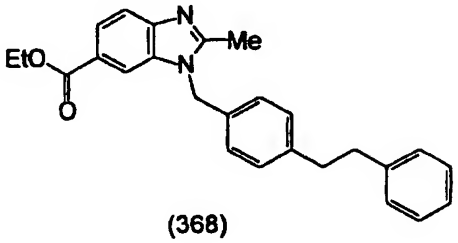

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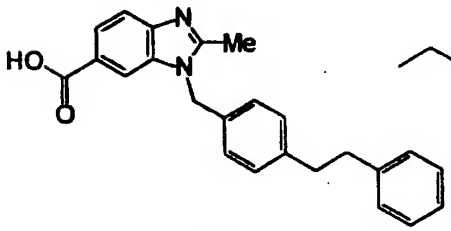

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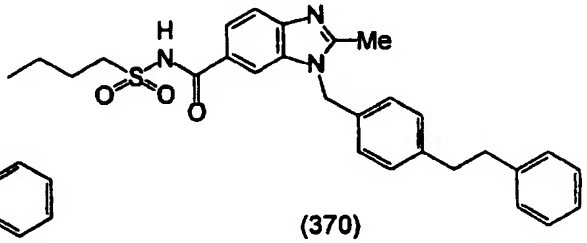
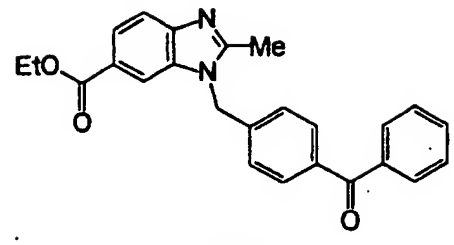
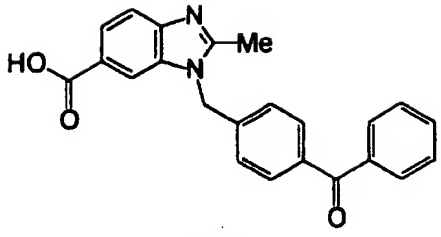


(370)

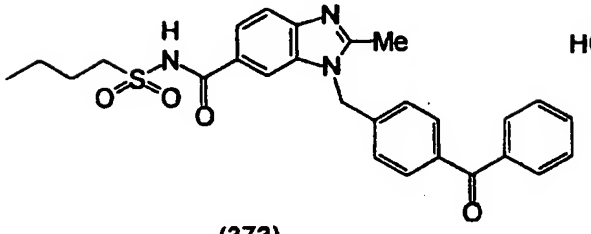
FIG. 56



(371)



(372)



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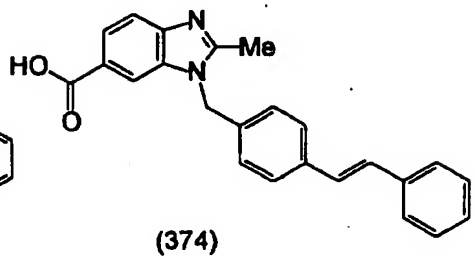
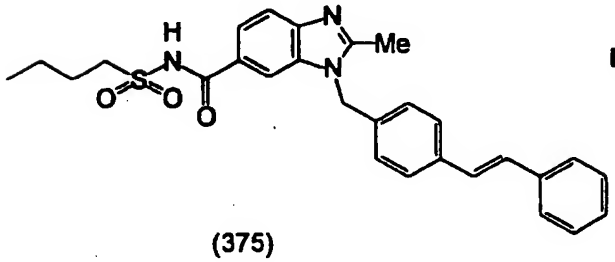
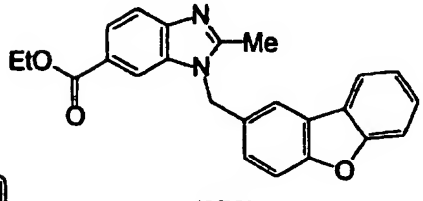


(374)

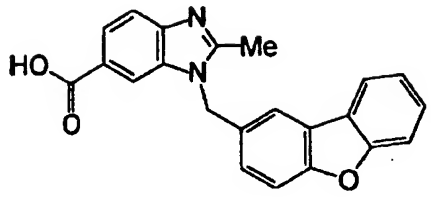


(375)

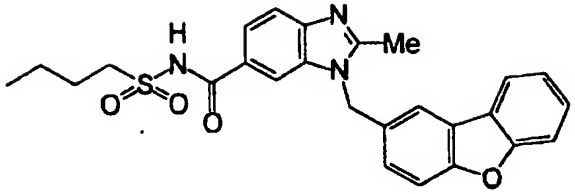


(376)

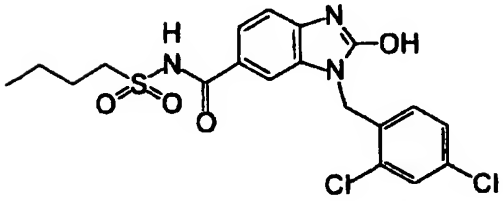
FIG. 57



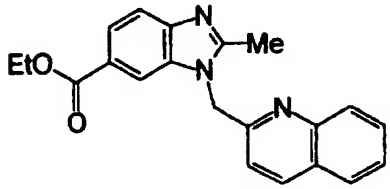
(377)



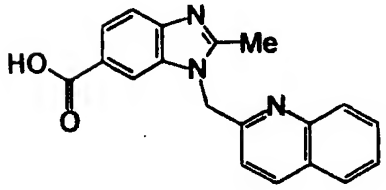
(378)



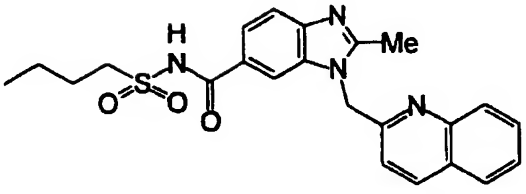
(379)



(380)

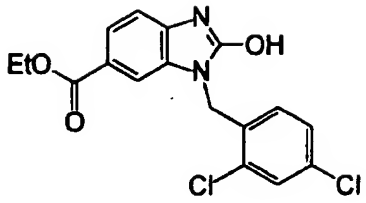


(381)

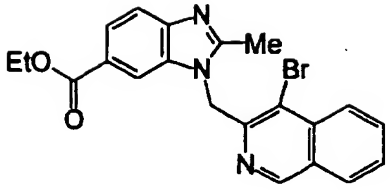


(382)

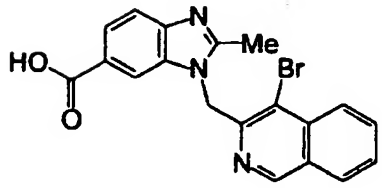
FIG. 58



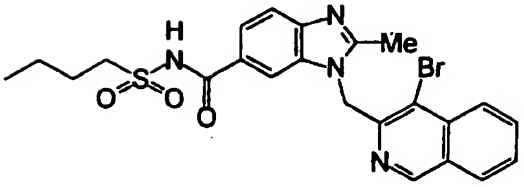
(383)



(384)



(385)



(386)

BENZIMIDAZOLE DERIVATIVES

TECHNICAL FIELD

The present invention relates to novel benzimidazole derivatives, and, more precisely, to novel benzimidazole derivatives and their pharmaceutically acceptable salts having blood sugar level-depressing activity or PDE5-inhibiting activity. The present invention also relates to pharmaceutical compositions comprising, as an active ingredient, such benzimidazole derivatives or their salts.

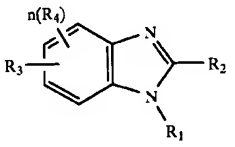
DISCLOSURE OF THE INVENTION

The subject matter of the present invention is to provide novel benzimidazole derivatives and their pharmaceutically acceptable salts, and also pharmaceutical compositions which comprise, as an active ingredient, such benzimidazole derivatives or their pharmaceutically acceptable salts, and which are useful for preventing and treating impaired glucose tolerance, diabetes (type II diabetes), diabetic complications (e.g., diabetic nephropathy, diabetic neuropathy, diabetic retinopathy, etc.), syndrome of insulin resistance (e.g., insulin receptor disorders, Rabson-Mendenhall syndrome, leprechaunism, Kobberling-Dunnigan syndrome, Seip syndrome, Lawrence syndrome, Cushing syndrome, acromegaly, etc.), hyperlipidemia, atherosclerosis, cardiovascular disorders (e.g., stenocardia, cardiac failure, etc.), hyperglycemia (e.g., abnormal saccharometabolism such as feeding disorders, etc.), or hypertension; or stenocardia, hypertension, pulmonary hypertension, congestive heart failure, glomerulopathy (e.g., diabetic glomerulosclerosis, etc.), tubulointerstitial disorders (e.g., renopathy induced by FK506, cyclosporin, etc.), renal failure, atherosclerosis, angiostenosis (e.g., after percutaneous arterioplasty), distal angiopathy, cerebral apoplexy, chronic reversible obstructions (e.g., bronchitis, asthma (chronic asthma, allergic asthma), etc.), allergic rhinitis, urticaria, glaucoma, diseases characterized by enteromotility disorders (e.g., hypersensitive enteropathy syndrome, etc.), impotence (e.g., organic impotence, psychic impotence, etc.), and diabetic complications (e.g., diabetic gangrene, diabetic arthropathy, diabetic glomerulosclerosis, diabetic dermatopathy, diabetic neuropathy, diabetic cataract, diabetic retinopathy, etc.), nephritis, cancerous cachexia, or restenosis after PTCA.

The present inventors provide pharmaceutical compositions comprising, as an active ingredient, any of benzimidazole derivatives of the following formulae (I) to (IV) and (VIII) to (XIV), and their pharmaceutically acceptable salts, which is usable for preventing and treating impaired glucose tolerance, diabetes (type II diabetes), diabetic complications such as diabetic nephropathy, diabetic neuropathy and diabetic retinopathy, syndrome of insulin resistance (e.g., insulin receptor disorders, Rabson-Mendenhall syndrome, leprechaunism, Kobberling-Dunnigan syndrome, Seip syndrome, Lawrence syndrome, Cushing syndrome, acromegaly, etc.), hyperlipidemia, atherosclerosis, cardiovascular disorders (e.g., stenocardia, cardiac failure, etc.), hyperglycemia (e.g., abnormal saccharometabolism such as feeding disorders, etc.), or hypertension; or stenocardia, hypertension, pulmonary hypertension, congestive heart failure, glomerulopathy (e.g., diabetic glomerulosclerosis, etc.), tubulointerstitial disorders (e.g., renopathy induced by FK506, cyclosporin, etc.), renal failure, atherosclerosis, angiostenosis (e.g., after percutaneous arterioplasty), distal angiopathy, cerebral apoplexy, chronic reversible obstructions (e.g., bronchitis, asthma (chronic asthma, allergic asthma), etc.), allergic rhinitis, urticaria, glaucoma, diseases

characterized by enteromotility disorders (e.g., hypersensitive enteropathy syndrome, etc.), impotence (e.g., organic impotence, psychic impotence, etc.), and diabetic complications (e.g., diabetic gangrene, diabetic arthropathy, diabetic glomerulosclerosis, diabetic dermatopathy, diabetic neuropathy, diabetic cataract, diabetic retinopathy, etc.), nephritis, cancerous cachexia, or restenosis after PTCA.

(I)



In formula (I);

R_1 represents a hydrogen atom, an arylsulfonyl group, or a lower alkyl group; said lower alkyl group may be substituted by an aryl group or an aryl group substituted by one or two substituents selected from a halogen atom, a haloaryl group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, a nitro group, an amino group, a cyano group, an aryl group, an aryl-lower alkyl group, an aryl-lower alkyloxy group, a haloaryl-lower alkyloxy group, an arylsulfonyl-lower alkyl group, an arylsulfonylamino group, a cyanoaryl group, and a heterocyclic group, or by a heterocyclic group;

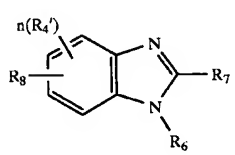
R_2 represents a hydrogen atom, a lower cycloalkyl group, a hydroxyl group, a lower alkoxy group, a mercapto group, a lower alkylthio group, an amino group, a lower alkylamino group, a carboxyl group, an aryl group, or a lower alkyl group; said lower alkyl group may be substituted by a halogen atom, a lower alkoxy group, a cyano group, a chlorocarbonyl group, an aryl group, or a heterocyclic group;

R_3 represents a carboxyl group, an esterified carboxyl group, an amidated carboxyl group, an amino group, an amido group, or a sulfonyl group; said amino group and said amido group may be substituted by an acyl group or a sulfonyl group; and a halogen atom, an amino group, or an acylamino group is bonded to said sulfonyl group; or R_3 may be bonded to the skeleton via a lower alkylene or alkenylene group;

R_4 represents a neutral substituent; and

n means an integer from 0 to 3.

(II)



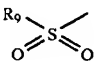
In formula (II);

R_6 represents an aryl-lower alkyl group or an aryl-lower alkyl group substituted by one or two substituents selected from a halogen atom, a haloaryl group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, a nitro group, an amino group, a cyano group, an aryl group, a cyanoaryl group, an aryl-lower alkyloxy group, an arylsulfonyl-lower alkyl group, an arylsulfonylamino group, an aryl-lower alkyl group, and a heterocyclic group;

R_7 represents a lower alkyl group or a lower cycloalkyl group;

R_8 represents a carbamoyl group, which may be substituted by a lower alkyl group, a lower alkyl group substituted by a substituted or unsubstituted aryl group or a substituted or unsubstituted heterocyclic group, an aryl group, a heterocyclic group, or a group of:

(IIa)



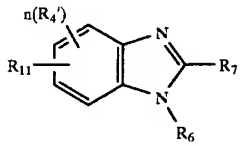
in which R_9 represents an alkyl group having up to 8 carbon atoms, a halo-lower alkyl group, an aryl-lower alkyl group, a hydroxy-lower alkyl group, a tri-lower alkylsilyl-lower alkyl group, a lower alkoxy-lower alkyl group, a lower alkylthio-lower alkyl group, a heterocyclic group, or an aryl group; said aryl group may be substituted by a halogen atom, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, or a nitro group;

or R_8 may be bonded to the skeleton via a lower alkylene or alkenylene group;

R_4' represents a hydrocarbon group or a halogenated hydrocarbon group; and

n means an integer from 0 to 3.

(III)



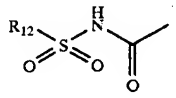
In formula (III);

R_6 represents an aryl-lower alkyl group or an aryl-lower alkyl group substituted by one or two substituents selected from a halogen atom, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, a nitro group, an amino group, a cyano group, an aryl group, a haloaryl group, a cyanoaryl group, an aryl-lower alkyloxy group, an arylsulfonyl-lower alkyl group, an arylsulfonylamino group, an aryl-lower alkyl group, and a heterocyclic group;

R_7 represents a lower alkyl group or a lower cycloalkyl group;

R_{11} represents a substitutent of a formula:

(IIIa)



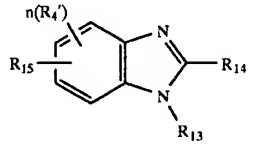
in which R_{12} represents an alkyl group having up to 8 carbon atoms, a halo-lower alkyl group, an aryl-lower alkyl group, a hydroxy-lower alkyl group, a tri-lower alkylsilyl-lower alkyl group, a lower alkoxy-lower alkyl group, a lower alkylthio-lower alkyl group, a heterocyclic group, or an aryl group; said aryl group may be substituted by a halogen atom, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, or a nitro group;

or R_{11} may be bonded to the skeleton via a lower alkylene or alkenylene group;

R_4' represents a hydrocarbon group or a halogenated hydrocarbon group; and

n means an integer from 0 to 3.

(IV)



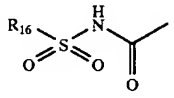
In formula (IV);

R_{13} represents an aryl-lower alkyl group or an aryl-lower alkyl group substituted by one or two substituents selected from a halogen atom, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, a nitro group, an amino group, a cyano group, an aryl group, a haloaryl group, a cyanoaryl group, an aryl-lower alkyl group, an arylsulfonyl-lower alkyl group, an arylsulfonylamino group, and a heterocyclic group;

R_{14} represents a lower alkyl group;

R_{15} represents a substitutent of a formula:

(IVa)

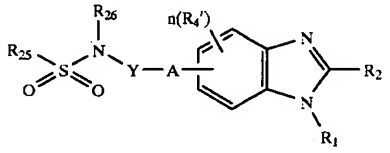


in which R_{16} represents a lower alkyl group or an aryl group;

R_4' represents a hydrocarbon group or a halogenated hydrocarbon group; and

n means an integer from 0 to 3.

(VIII)



In formula (VIII);

R_1 represents a hydrogen atom, an arylsulfonyl group, or a lower alkyl group; said lower alkyl group may be substituted by an aryl group or an aryl group substituted by one or two substituents selected from a halogen atom, a haloaryl group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, a nitro group, an amino group, a cyano group, an aryl group, an aryl-lower alkyloxy group, an arylsulfonyl-lower alkyl group, an aryl-lower alkyl group, a haloaryl-lower alkyloxy group, an arylsulfonylamino group, an arylcarbonylamino group, an arylcarbonyl group, an arylalkenyl group, a cyanoaryl group, and a heterocyclic group, or by a heterocyclic group;

R_2 represents a hydrogen atom, a lower cycloalkyl group, a hydroxyl group, a hydroxy-lower alkyl group, a lower alkoxy group, a mercapto group, a lower alkylthio group, an amino group, a lower alkylamino group, a

carboxyl group, an aryl group, or a lower alkyl group; said lower alkyl group may be substituted by a halogen atom, a lower alkoxy group, a cyano group, a halocarbonyl group, an aryl group, or a heterocyclic group;

R_{25} represents an alkyl group having up to 8 carbon atoms, a lower cycloalkyl group, a halo-lower alkyl group, a tri-lower alkylsilyl-lower alkyl group, a lower alkoxy-lower alkyl group, a lower alkylthio-lower alkyl group, an aryl group, a heterocyclic group, an aryl-lower alkyl group, or a hydroxy-lower alkyl group; said aryl group may be substituted by a halogen atom, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, or a nitro group;

R_{26} represents a hydrogen atom or a lower alkyl group; provided that, when R_{25} and R_{26} are both lower alkyl groups, they may be bonded together to form a ring;

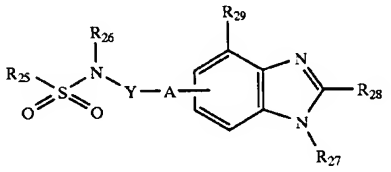
Y represents a carbonyl group or a lower alkylene group;

A represents a single bond, or a lower alkylene or alkenylene group;

R_4' represents a hydrocarbon group or a halogenated hydrocarbon group; and

n means an integer from 0 to 3.

(IX)



In formula (IX);

R_{27} represents a hydrogen atom, an alkyl group having up to 7 carbon atoms, a halo-lower alkyl group, an arylsulfonyl group, an aryl-lower alkyl group, a heterocyclic lower alkyl group, or a halo-heterocyclic lower alkyl group; and the aromatic ring moiety in said aryl-lower alkyl group may be substituted by one or two substituents selected from a halogen atom, a lower alkyl group, a halo-lower alkyl group, a cyanoaryl group, an amino group, a lower alkoxy group, a nitro group, a cyano group, an aryl group, a haloaryl group, an arylsulfonyl-lower alkyl group, an arylsulfonylamino group, an aryl-lower alkyloxy group, an aryl-lower alkyl group, a heterocyclic group, an aryloxy group, an arylcarbonyl group, an arylcarbonylamino group, and an aryl-lower alkyloxy group substituted by one or two halogen atoms;

R_{28} represents a hydrogen atom, an alkyl group having up to 7 carbon atoms, a halo-lower alkyl group, a lower alkoxy-lower alkyl group, a lower cycloalkyl group, an aryl group, an aryl-lower alkyl group, a lower alkylamino group, a lower alkoxy group, a lower alkylthio group, a hydroxyl group, a mercapto group, an amino group, or a carboxyl group;

R_{25} represents an alkyl group having up to 8 carbon atoms, a halo-lower alkyl group, a tri-lower alkylsilyl-lower alkyl group, a lower alkoxy-lower alkyl group, a lower alkylthio-lower alkyl group, an aryl group, a heterocyclic group, an aryl-lower alkyl group, or a hydroxy-lower alkyl group; and said aryl group may be substituted by a halogen atom, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, or a nitro group;

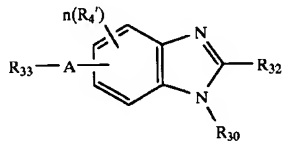
R_{26} represents a hydrogen atom or a lower alkyl group; provided that, when R_{25} and R_{26} are both lower alkyl groups, they may be bonded together to form a ring;

Y represents a carbonyl group or a lower alkylene group;

A represents a single bond, or a lower alkylene or alkenylene group; and

R_{29} represents a hydrogen atom or a lower alkyl group.

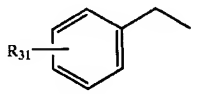
(X)



In formula (X);

R_{30} represents a hydrogen atom, a lower alkyl group, a substituted or unsubstituted aryl-lower alkyl group of a formula:

(Xa)



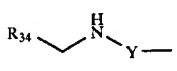
in which R_{31} represents a hydrogen atom, a cyanoaryl group, an amino group, a lower alkoxy group, a nitro group, a cyano group, an aryl group, a haloaryl group, an arylsulfonyl-lower alkyl group, an arylsulfonylamino group, an aryl-lower alkyloxy group, an aryl-lower alkyl group, a heterocyclic group, or an aryloxy group,

or represents an aryl-lower alkyloxy group or an aryl-lower alkyloxy group substituted by one or two halogen atoms, an arylsulfonyl group, a heterocyclic lower alkyl group, an arylcarbonylamino group, an arylcarbonyl group, an arylalkenyl group, or a lower alkylenedioxyaryl group; and the alkyl moiety in said aryl-lower alkyl group may be substituted by a lower alkyl group;

R_{32} represents a hydrogen atom, a lower alkyl group, a halo-lower alkyl group, a lower cycloalkyl group, an aryl group, an aryl-lower alkyl group, a lower alkylamino group, a lower alkoxy group, a lower alkylthio group, a lower alkoxy-lower alkyl group, or a heterocyclic lower alkyl group;

R_{33} represents a carboxyl group, a lower alkoxycarbonyl group, a (2-cyanoaryl)oxycarbonyl group, or a group of a formula:

(Xb)



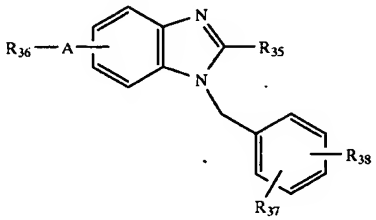
in which Y represents a carbonyl group or a lower alkylene group; R_{34} represents a lower alkyl group or a lower alkyl group substituted by a substituted or unsubstituted aryl or heterocyclic group, or represents an aryl group or a heterocyclic group;

A represents a single bond, or a lower alkylene or alkenylene group;

R_4' represents a hydrocarbon group or a halogenated hydrocarbon group. R_4' may include an alkyl group, an

aralkyl group, an alkynyl group, and halogenated groups of these. R_4' may be either saturated or unsaturated, may be either linear or cyclic, and may even be branched, as the case may be. For the halogenated groups, the type of the halogen therein is not specifically defined, and the number of the halogen substituents therein is not also specifically defined. n means an integer from 0 to 3. Therefore, one, two or three R_4's may be bonded to the skeleton, or no R_4' may be bonded thereto. The position of R_4' is not specifically defined and may be any of the ortho-position, the meta-position and the para-position relative to the other substituent. However, when R_{30} is a hydrogen atom, n is 0, or that is, no R_4' is bonded to the skeleton.

(XI)



In formula (XI);

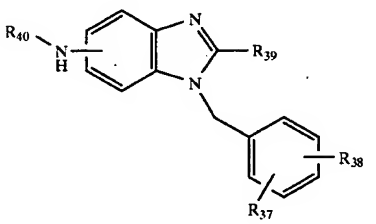
R_{35} represents a hydrogen atom, an aryl group, a lower alkoxy-lower alkyl group, a lower alkyl group, or an aryl-lower alkyl group;

R_{36} represents a carboxyl group, a lower alkoxycarbonyl group, a heterocyclic lower alkylamino group, or a heterocyclic lower alkylcarbamoyl group;

R_{37} and R_{38} each independently represent a hydrogen atom, a halogen atom, a lower alkyl group, a halo-lower alkyl group, an aryl group, an aryl-lower alkyl group, or an aryl-lower alkyloxy group; and

A represents a single bond, or a lower alkylene or alkenylene group; provided that, when R_{35} is a lower alkyl group, A is a lower alkylene group or a lower alkenylene group.

(XII)



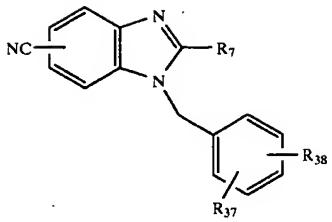
In formula (XII);

R_{37} and R_{38} each independently represent a hydrogen atom, a halogen atom, a lower alkyl group, a halo-lower alkyl group, an aryl group, an aryl-lower alkyl group, or an aryl-lower alkyloxy group;

R_{39} represents a lower alkyl group; and

R_{40} represents a hydrogen atom, a lower alkoxycarbonyl group, a lower alkanoyl group, a lower alkanesulfonyl group, or a carbamoyl group.

(XIII)

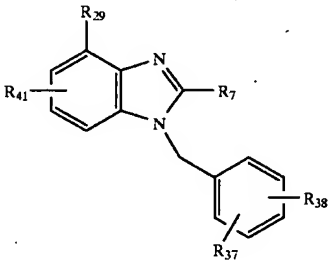


In formula (XIII);

R_{37} and R_{38} each independently represent a hydrogen atom, a halogen atom, a lower alkyl group, a halo-lower alkyl group, an aryl group, an aryl-lower alkyl group, or an aryl-lower alkyloxy group; and

R_7 represents a lower alkyl group or a lower cycloalkyl group.

(XIV)



In formula (XIV);

R_{37} and R_{38} each independently represent a hydrogen atom, a halogen atom, a lower alkyl group, a halo-lower alkyl group, an aryl group, an aryl-lower alkyl group, or an aryl-lower alkyloxy group;

R_7 represents a lower alkyl group or a lower cycloalkyl group;

R_{41} represents a 2-pyridylcarbamoyl group, a 2-carboxy-1-pyrrolidinocarbonyl group, an N-methyl-N-(2-pyridylmethyl)carbamoyl group, a homopiperidinocarbonyl group, a [2-(N-oxo)-pyridylmethyl]carbamoyl group, a 4-(dimethylamino)benzylcarbamoyl group, a piperonylcarbamoyl group, an N-methyl-N-(2-pyridyl) carbamoyl group, a thiomorpholinocarbonyl group, a halosulfonyl group, an aminosulfonyl group, an acylaminosulfonyl group, a lower alkoxycarbonyl group, or a carboxyl group;

R_{29} represents a hydrogen atom, or a lower alkyl group; provided that, when R_{41} is a lower alkylcarbonyl group or a carboxyl group, R_{29} is a lower alkyl group.

The present invention also provides novel benzimidazole derivatives of the above-mentioned (VIII) to (XIV) and their salts.

Benzimidazole derivatives to be provided by the present invention can be produced according to the following reaction formulae (a) to (f):

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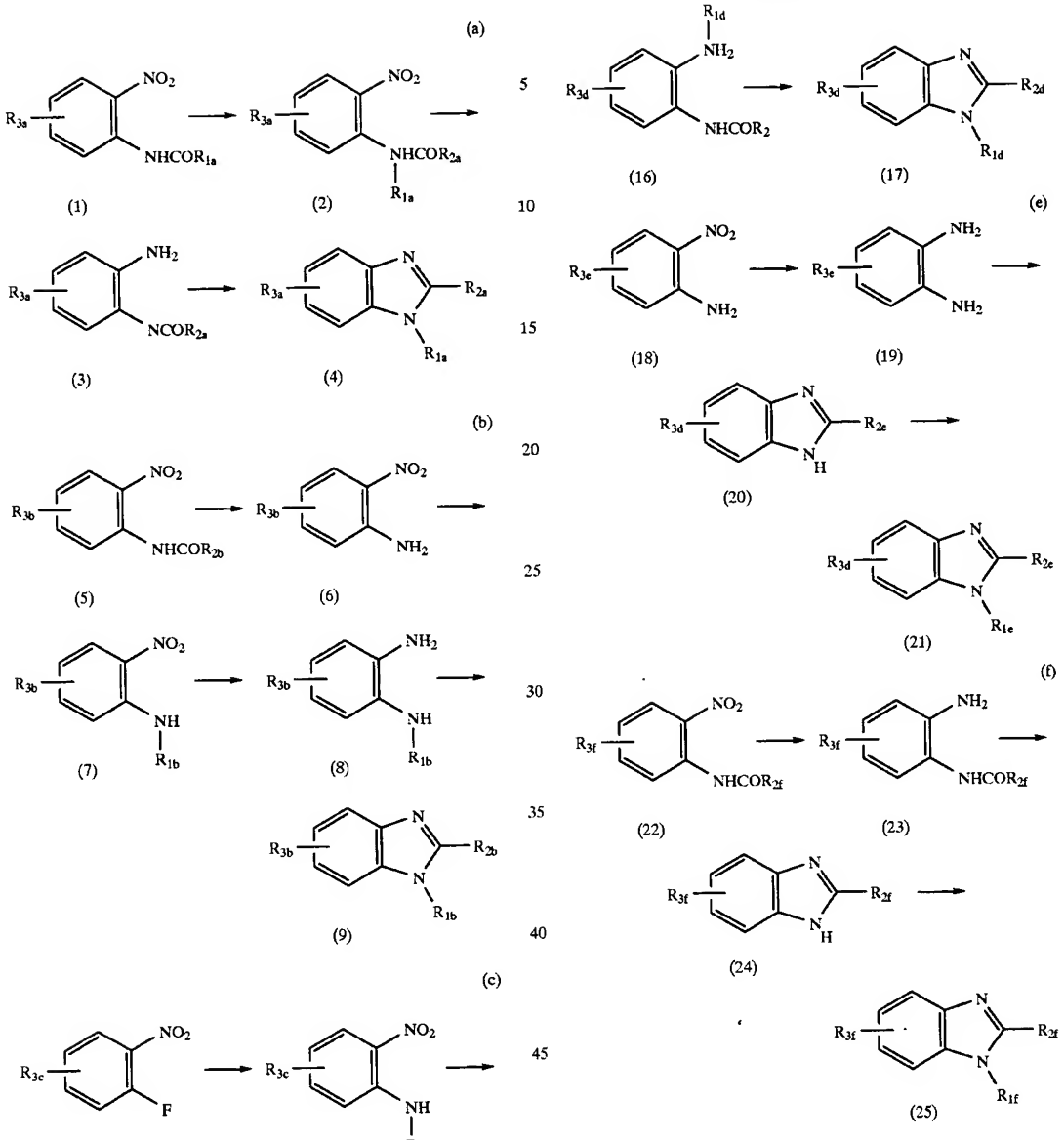
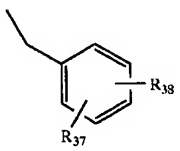
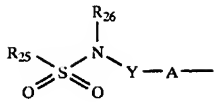


In the above-mentioned reaction formulae, R_{1a} to R_{1f} may be selected from the above-mentioned R_1, R_6, R_{13}, R_{17}, R_{22}, R_{23}, R_{27}, R_{30}, or a substituted benzyl group of a formula:

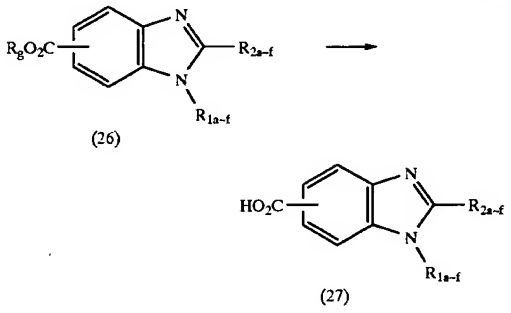


wherein R_{37} and R_{38} have the same meanings as those mentioned above. R_{2a} to R_{2f} may be selected from the above-mentioned R_2, R_7, R_{14}, R_{18}, R_{28}, R_{32}, R_{35} or R_{39}. The substituents R_{3a} to R_{3f} may be selected from a substituent of a formula:



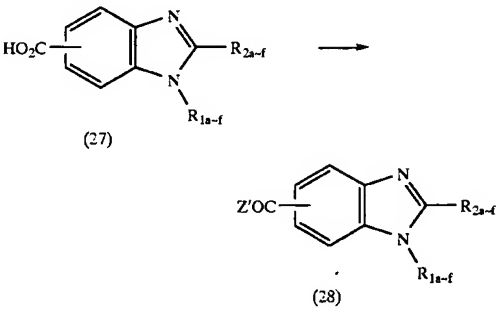
with R_{25}, R_{26}, Y and A having the same meanings as those mentioned above, or from the above-mentioned R_3, R_8, R_{11}, R_{15}, R_{19}, R_{24}, AR_{33}, AR_{36}, NHR_{40}, CN or R_{41}. The substituents that define R_{3a} through R_{3f} can be mutually converted to each other. For example, as in the step (g) or (h) mentioned below, the ester (26) can be converted into the corresponding acid (27) or acid halide (28). The desired benzimidazoles can be produced through the reaction of these compounds with amines or sulfonamides. It is further possible to give various derivatives, as in the step (i) or (j) or (k) or (l) or (m) or (n) mentioned below. Such conversion of the groups, R_{3a} through R_{3f} can be effected at any stage in the steps (a) through (f), while depending on the stability of R_{1a} to R_{1f} as well as R_{2a} to R_{2f} in the compounds and even on the easiness in the isolation of the products formed.

(g)



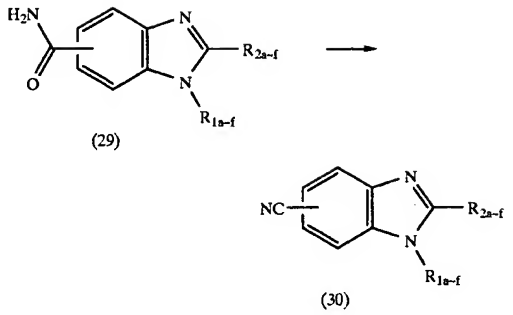
In this reaction formula, R_9 represents a lower alkyl group; and $R_{1a\text{-}f}$ and $R_{2a\text{-}f}$ have the same meanings as those mentioned above.

(g)



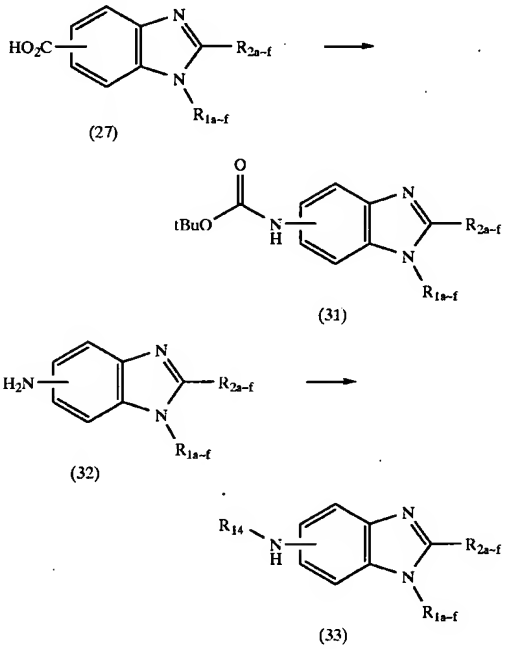
In this reaction formula, Z' represents a chlorine atom or a bromine atom; and $R_{1a\text{-}f}$ and $R_{2a\text{-}f}$ have the same meanings as those mentioned above.

(i)



In this reaction formula, $R_{1a\text{-}f}$ and $R_{2a\text{-}f}$ have the same meanings as those mentioned above.

(j)



In this reaction formula, $R_{1a\text{-}f}$ and $R_{2a\text{-}f}$ have the same meanings as those mentioned above.

In the reaction step (a), a compound of formula (1) may be reacted with a base, such as sodium hydride, lithium diisopropylamide, lithium hydrogencarbonate, lithium carbonate, lithium hydroxide, sodium hydrogencarbonate, sodium carbonate, sodium hydroxide, potassium hydrogencarbonate, potassium carbonate, potassium hydroxide or the like, and with a compound to be represented by $R_{1a}Z$ (where Z represents a chlorine atom, a bromine atom, a toluenesulfonyloxy group, or a methanesulfonyloxy group) to give a compound of formula (2). The compound of formula (2) may be 1) reduced with reduced iron or zinc under an acidic condition, or 2) reduced with a transition metal catalyst, such as typically palladium, platinum, ruthenium or nickel, in a hydrogen atmosphere, or 3) reduced with a transition metal catalyst, such as typically palladium, platinum, ruthenium or nickel, in the presence of formic acid, or 4) reduced with sodium hydrosulfite, to be

converted into a compound of formula (3). In the process 1), the compound of formula (3) is often cyclized in the reaction system directly into a compound of formula (4). Depending on the compound of formula (2) being reduced, the compound of formula (4) may be partly formed in any of the processes 1) to 4). The compound of formula (3) may be processed with a carboxylic acid, a sulfonic acid or an inorganic acid, such as acetic acid, p-toluenesulfonic acid, hydrochloric acid, sulfuric acid, phosphoric acid or the like, to give the compound of formula (4).

In the step (b), a compound of formula (5) is may be hydrolyzed or solvolyzed with a base, such as lithium hydrogencarbonate, lithium carbonate, lithium hydroxide, sodium hydrogencarbonate, sodium carbonate, sodium hydroxide, potassium hydrogencarbonate, potassium carbonate, potassium hydroxide or the like, or with a carboxylic acid, a sulfonic acid or inorganic acid, such as acetic acid, p-toluenesulfonic acid, hydrochloric acid, sulfuric acid, phosphoric acid or the like, into a compound of formula (6). The compound of formula (6) may be reacted with a base, such as sodium hydride, lithium diisopropylamide, lithium hydrogencarbonate, lithium carbonate, lithium hydroxide, sodium hydrogencarbonate, sodium carbonate, sodium hydroxide, potassium hydrogencarbonate, potassium carbonate, potassium hydroxide or the like, and with a compound to be represented by $R_{1b}Z$ (where Z represents a chlorine atom, a bromine atom, a toluenesulfonyloxy group, or a methanesulfonyloxy group) to give a compound of formula (7). The compound of formula (7) may be 1) reduced with reduced iron or zinc under an acidic condition, or 2) reduced with a transition metal catalyst, such as typically palladium, platinum, ruthenium or nickel, in a hydrogen atmosphere, or 3) reduced with a transition metal catalyst, such as typically palladium, platinum, ruthenium or nickel, in the presence of formic acid, or 4) reduced with sodium hydrosulfite, to be converted into a compound of formula (8). A compound of formula (9) can be produced from the compound of formula (8) and the corresponding carboxylic acid or acid chloride or acid bromide or acid anhydride.

In the step (c), a compound of formula (11) can be produced from a compound of formula (10) and a compound to be represented by $R_{1c}NH_2$. The conversion of the compound of formula (11) to a compound of formula (13) is the same as that of the compound of formula (7) to the compound of formula (9) in the step (b).

In the step (d), a compound of formula (14) may be 1) reduced with a transition metal catalyst such as typically palladium, platinum, ruthenium or nickel in a hydrogen atmosphere, or 2) reduced with sodium hydrosulfite to give a compound of formula (15). The compound of formula (15) may be reacted with a base, such as lithium hydrogencarbonate, lithium carbonate, lithium hydroxide, sodium hydrogencarbonate, sodium carbonate, sodium hydroxide, potassium hydrogencarbonate, potassium carbonate, potassium hydroxide or the like, and with a compound to be represented by $R_{1d}Z$ (where Z represents a chlorine atom, a bromine atom, a toluenesulfonyloxy group, or a methanesulfonyloxy group) to give a compound of formula (16). The compound of formula (16) may be treated with a carboxylic acid, a sulfonic acid or an inorganic acid, such as acetic acid, p-toluenesulfonic acid, hydrochloric acid, sulfuric acid, phosphoric acid or the like, to give a compound of formula (17).

In the step (e), a compound of formula (18) may be (1) reduced with reduced iron or zinc under an acidic condition, or 2) reduced with a transition metal catalyst, such as typically palladium, platinum, ruthenium or nickel, in a hydrogen atmosphere, or 3) reduced with a transition metal catalyst, such as typically palladium, platinum, ruthenium or nickel, in the presence of formic acid, or 4) reduced with sodium hydrosulfite, to be converted into a compound of formula (19). A compound of formula (20) can be produced from the compound of formula (19) and the corresponding carboxylic acid or acid anhydride or acid chloride or acid bromide. The compound of formula (20) may be reacted with a base, such as sodium hydride, lithium diisopropylamide, lithium hydrogencarbonate, lithium carbonate, lithium hydroxide, sodium hydrogencarbonate, sodium carbonate, sodium hydroxide, potassium hydrogencarbonate, potassium carbonate, potassium hydroxide or the like, and with a compound to be represented by $R_{1e}Z$ (where Z represents a chlorine atom, a bromine atom, a toluenesulfonyloxy group, or a methanesulfonyloxy group) to give a compound of formula (21).

In the process comprising the above-mentioned step, in general, the product may be obtained as a mixture comprising the compound of formula (21) where R_{3e} is positioned in the 5-position and that where it is in the 6-position, or a mixture comprising the compound of formula (21) where R_{3e} is positioned in the 4-position and that where it is in the 7-position. Each compound of formula (21) can be purified from the mixture as the single compound, for example, through recrystallization, column chromatography, thin-layer chromatography, high-performance liquid chromatography or the like.

In the step (f), a compound of formula (22) may be 1) reduced with reduced iron or zinc under an acidic condition, or 2) reduced with a transition metal catalyst, such as typically palladium, platinum, ruthenium or nickel, in a hydrogen atmosphere, or 3) reduced with a transition metal catalyst, such as typically palladium, platinum, ruthenium or nickel, in the presence of formic acid, or 4) reduced with sodium hydrosulfite, to be converted into a compound of formula (23). In the process 1), the compound of formula (23) is often cyclized in the reaction system directly into a compound of formula (24). Depending on the compound of formula (22) being reduced, the compound of formula (24) may be partly formed in any of the processes 1) to 4). The compound of formula (23) may be processed with a carboxylic acid, a sulfonic acid or an inorganic acid, such as acetic acid, p-toluenesulfonic acid, hydrochloric acid, sulfuric acid, phosphoric acid or the like, to give the compound of formula (24). The compound of formula (24) may be converted into a benzimidazole compound of formula (25) in the same manner as in the step (e) of converting the compound of formula (20) into the compound of formula (21). In this step, in general, the product may be obtained as a mixture comprising the compound of formula (25) where R_{3f} is positioned in the 5-position and that where it is in the 6-position, or a mixture comprising the compound of formula (25) where R_{3f} is positioned in the 4-position and that where it is in the 7-position. Each compound of formula (25) can be purified from the mixture as the single compound, for example, through recrystallization, column chromatography, thin-layer chromatography, high-performance liquid chromatography or the like.

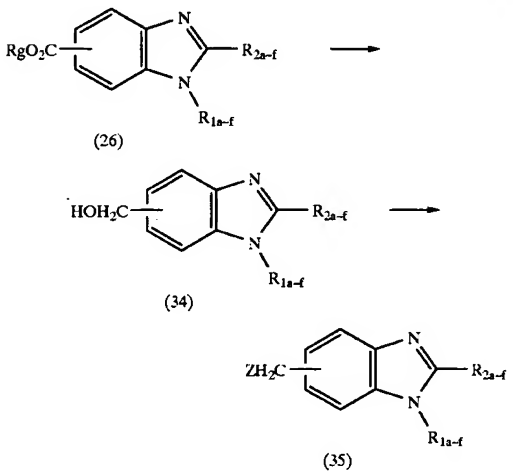
In the step (g), a compound of formula (26) may be hydrolyzed with a base, such as lithium hydroxide, sodium hydroxide, potassium hydroxide or the like, to give a compound of formula (27). The compound of formula (27) may be reacted with a carbonyldiimidazole and then with amines or sulfonamides in the presence of a base to give different benzimidazole derivatives.

In the step (h), the compound of formula (27) may be processed with thionyl chloride or thionyl bromide or phosphorus trichloride or phosphorus pentachloride or phosphorus oxychloride to be converted into its acid halide of formula (28). The compound of formula (28) may be reacted with amines or sulfonamides to give different benzimidazole derivatives.

In the step (i), a compound of formula (29) may be reacted with titanium tetrachloride to give a compound of formula (30).

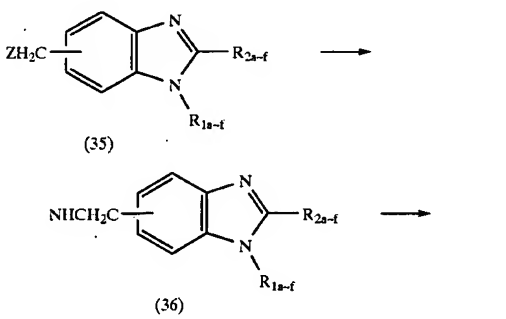
In the step (j), the compound of formula (27) may be reacted with an azide, such as typically diphenylphosphorylazide, in the presence of an alcohol, such as typically t-butanol, to give a compound of formula (31). The compound of formula (31) may be decomposed with an acid to give a compound of formula (32). The compound of formula (32) may be reacted with a compound to be represented by $R_{40}Z$ (where Z represents a chlorine atom or a bromine atom) to give a compound of formula (33).

(k)



wherein R_g, $R_{1a\text{-}f}$ and $R_{2a\text{-}f}$ have the same meanings as those mentioned above; and Z represents a chlorine atom, a bromine atom, a toluenesulfonyloxy group, or a methanesulfonyloxy group.

(l)



wherein $R_{1a\text{-}f}$, $R_{2a\text{-}f}$ and Z have the same meanings as those mentioned above.

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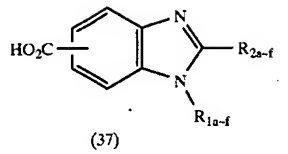
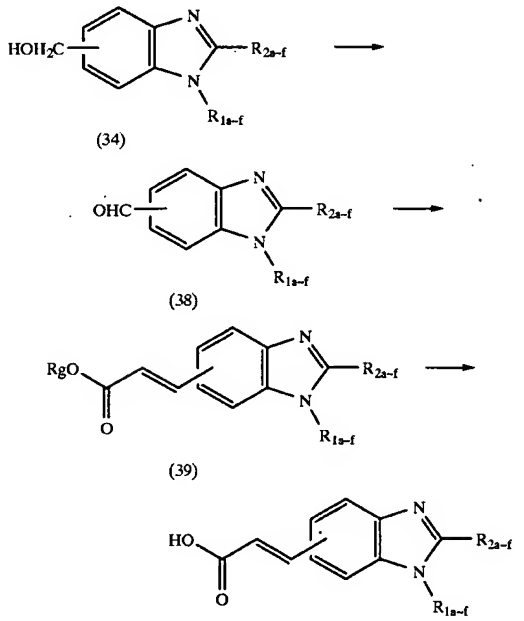


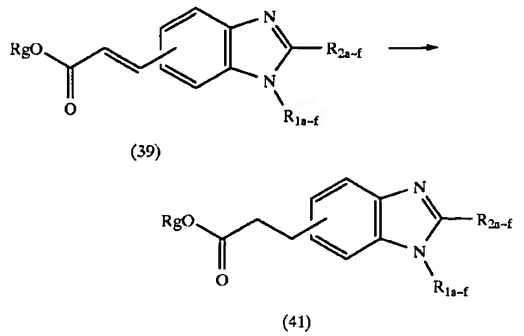
(37)

(m)



wherein $R_{1a\text{-}f}$, $R_{2a\text{-}f}$ and R_9 have the same meanings as those mentioned above.

(n)



wherein $R_{1a\text{-}f}$, $R_{2a\text{-}f}$ and R_9 have the same meanings as those mentioned above.

In the step (k), the compound of formula (26) may be reduced into a compound of formula (34), which may be then treated with thionyl chloride, thionyl bromide, phosphorus oxychloride, phosphorus oxybromide, phosphorus trichloride, phosphorus pentachloride, methanesulfonyl

chloride, toluenesulfonyl chloride or the like to be converted into a compound of formula (35).

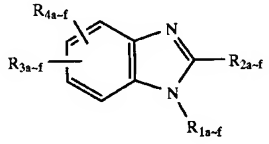
In the step (l), the compound of formula (35) may be reacted with sodium cyanide or potassium cyanide to give a compound of formula (36), which may be then hydrolyzed with lithium hydroxide or sodium hydroxide or potassium hydroxide to give a carboxylic acid of formula (37).

In the step (m), a compound of formula (38) to be obtained by oxidizing the compound of formula (34) may be reacted with an alkyl(triphenylphosphoranilidene)acetate to give a compound of formula (39), which may then be hydrolyzed with lithium hydroxide or sodium hydroxide or potassium hydroxide to give a carboxylic acid of formula (40). The compound of formula (35), (37) or (40) may be reacted with amines or sulfonylamides to give different benzimidazole compounds.

In the step (n), the compound of formula (39) may be reduced with palladium, platinum, ruthenium or the like transition metal catalyst in a hydrogen atmosphere or in the presence of formic acid to give a compound of formula (41).

The following compounds of:

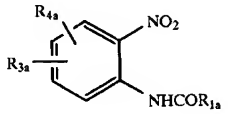
(1')



where $R_{1a\text{-}f}$, $R_{2a\text{-}f}$ and $R_{3a\text{-}f}$ have the same meanings as those mentioned above; and $R_{4a\text{-}f}$ may be selected from the above-mentioned R_4, R_4' and R_{29},

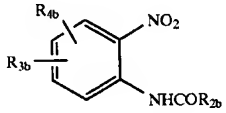
can be produced according to the steps (a) to (f) while starting from the following compounds of:

(2')



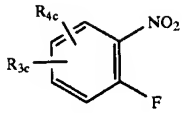
where R_{1a}, R_{2a} and R_{3a} have the same meanings as those mentioned above; and R_{4a} may be selected from the above-mentioned R_4, R_4' and R_{29};

(3')



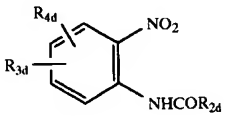
where R_{1b}, R_{2b} and R_{3b} have the same meanings as those mentioned above; and R_{4b} may be selected from the above-mentioned R_4, R_4' and R_{29};

(4')



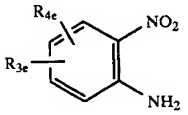
where R_{1c}, R_{2c} and R_{3c} have the same meanings as those mentioned above; and R_{4c} may be selected from the above-mentioned R_4, R_4' and R_{29};

(5')



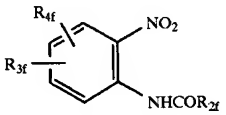
where R_{1d}, R_{2d} and R_{3d} have the same meanings as those mentioned above; and R_{4d} may be selected from the above-mentioned R_4, R_4' and R_{29};

(6')



where R_{1e}, R_{2e} and R_{3e} have the same meanings as those mentioned above; and R_{4e} may be selected from the above-mentioned R_4, R_4' and R_{29};

(7')



where R_{1f}, R_{2f} and R_{3f} have the same meanings as those mentioned above; and R_{4f} may be selected from the above-mentioned R_4, R_4' and R_{29}.

If desired, the intermediates formed in the above-mentioned steps may optionally be purified, prior to being subjected to the next step, through any conventional purification including, for example, recrystallization, column chromatography, thin-layer chromatography, high-performance liquid chromatography and the like. If also desired, the final products of the compounds of the present invention may optionally be purified through any conventional purification which is employed in the art of purifying organic compounds and which includes, for example, recrystallization, column chromatography, thin-layer chromatography, high-performance liquid chromatography and the like. To identify these compounds, employable is any of NMR spectrography, mass spectrography, IR spectrography, elementary analysis, measurement of melting point and others.

Preferred embodiments and their details of various definitions as referred to herein to be within the scope of the present invention are described below.

Unless otherwise specifically indicated herein, the terminology "lower" indicates that the group has from 1 to 6

carbon atoms. As preferred examples of the lower alkyl group as referred to herein, mentioned are linear or branched alkyl groups including a methyl group, an ethyl group, an n-propyl group, an i-propyl group, an n-butyl group, an i-butyl group, a sec-butyl group, a t-butyl group, an n-pentyl group, an i-pentyl group, a sec-pentyl group, a t-pentyl group, a 2-methylbutyl group, an n-hexyl group, a 1-methylpentyl group, a 2-methylpentyl group, a 3-methylpentyl group, a 4-methylpentyl group, a 1-ethylbutyl group, a 2-ethylbutyl group, a 1,1-dimethylbutyl group, a 2,2-dimethylbutyl group, a 3,3-dimethylbutyl group, a 1-ethyl-1-methyl propyl groups, etc.

The alkyl group having up to 7 carbon atoms is a linear or branched alkyl group, including a methyl group, an ethyl group, an n-propyl group, an i-propyl group, an n-butyl group, an i-butyl group, a sec-butyl group, a t-butyl group, an n-pentyl group, an i-pentyl group, a sec-pentyl group, a t-pentyl group, a 2-methylbutyl group, an n-hexyl group, a 1-methylpentyl group, a 2-methylpentyl group, a 3-methylpentyl group, a 4-methylpentyl group, a 1-ethylbutyl group, a 2-ethylbutyl group, a 3-ethylbutyl group, a 1,1-dimethylbutyl group, a 2,2-dimethylbutyl group, a 3,3-dimethylbutyl group, a 1-ethyl-1-methylpropyl group, an n-heptyl group, a 1-methylhexyl group, a 2-methylhexyl group, a 3-methylhexyl group, a 4-methylhexyl group, a 5-methylhexyl group, a 1-ethylpentyl group, a 2-ethylpentyl group, a 3-ethylpentyl group, a 4-ethylpentyl group, a 1,1-dimethylpentyl group, a 2,2-dimethylpentyl group, a 3,3-dimethylpentyl group, a 4,4-dimethylpentyl group, a 1-propylbutyl group, etc.

The alkyl group having up to 8 carbon atoms is a linear or branched alkyl group, including a methyl group, an ethyl group, an n-propyl group, an i-propyl group, an n-butyl group, an i-butyl group, a sec-butyl group, a t-butyl group, an n-pentyl group, an i-pentyl group, a sec-pentyl group, a t-pentyl group, a 2-methylbutyl group, an n-hexyl group, a 1-methylpentyl group, a 2-methylpentyl group, a 3-methylpentyl group, a 4-methylpentyl group, a 1-ethylbutyl group, a 2-ethylbutyl group, a 3-ethylbutyl group, a 1,1-dimethylbutyl group, a 2,2-dimethylbutyl group, a 3,3-dimethylbutyl group, a 1-ethyl-1-methylpropyl group, an n-heptyl group, a 1-methylhexyl group, a 2-methylhexyl group, a 3-methylhexyl group, a 4-methylhexyl group, a 5-methylhexyl group, a 1-ethylpentyl group, a 2-ethylpentyl group, a 3-ethylpentyl group, a 4-ethylpentyl group, a 1,1-dimethylpentyl group, a 2,2-dimethylpentyl group, a 3,3-dimethylpentyl group, a 4,4-dimethylpentyl group, a 1-propylbutyl group, an n-octyl group, a 1-methylheptyl group, a 2-methylheptyl group, a 3-methylheptyl group, a 4-methylheptyl group, a 5-methylheptyl group, a 6-methylheptyl group, a 1-ethylhexyl group, a 2-ethylhexyl group, a 3-ethylhexyl group, a 4-ethylhexyl group, a 5-ethylhexyl group, a 1,1-dimethylhexyl group, a 2,2-dimethylhexyl group, a 3,3-dimethylhexyl group, a 4,4-dimethylhexyl group, a 5,5-dimethylhexyl group, a 1-propylpentyl group, a 2-propylpentyl group, etc.

The lower alkylene group is an alkylene group having 6 or less carbon atoms, including a methylene group, an ethylene group, a propylene group, a butylene group, a pentylene group, a hexylene group, etc. The lower alkenylene group is an alkenylene group having 6 or less carbon atoms, including an ethenylene group, a 1-propenylene group, a 2-propenylene group, a 1-butenylene group, a 2-butenylene group, a 3-butenylene group, a 1-pentenylene group, a 2-pentenylene group, a 3-pentenylene group, a 4-pentenylene group, a 1-hexenylene group, a 2-hexenylene group, a 3-hexenylene group, a 4-hexenylene group, a 5-hexenylene group, etc.

The halogen atom includes a fluorine atom, a chlorine atom, a bromine atom and an iodine atom. Preferred are a fluorine atom, a chlorine atom and a bromine atom.

The halo-lower alkyl group is a linear or branched alkyl group having up to 8 carbon atoms, which is substituted with one or more halogen atoms selected from fluorine, chlorine, bromine and iodine atoms. Preferred is a linear or branched alkyl group having up to 8 carbon atoms, which is substituted with one or more halogen atoms selected from fluorine, chlorine and bromine atoms. It includes, for example, a fluoromethyl group, a difluoromethyl group, a trifluoromethyl group, a chloromethyl group, a dichloromethyl group, a trichloromethyl group, a bromomethyl group, a dibromomethyl group, a tribromomethyl group, a 1-fluoroethyl group, a 1-chloroethyl group, a 1-bromoethyl group, a 2-fluoroethyl group, a 2-chloroethyl group, a 2-bromoethyl group, a 1,2-difluoroethyl group, a 1,2-dichloroethyl group, a 1,2-dibromoethyl group, a 2,2,2-trifluoroethyl group, a heptafluoroethyl group, a 1-fluoropropyl group, a 1-chloropropyl group, a 1-bromopropyl group, a 2-fluoropropyl group, a 2-chloropropyl group, a 2-bromopropyl group, a 3-fluoropropyl group, a 3-chloropropyl group, a 3-bromopropyl group, a 1,2-difluoropropyl group, a 1,2-dichloropropyl group, a 1,2-dibromopropyl group, a 2,3-difluoropropyl group, a 2,3-dichloropropyl group, a 2,3-dibromopropyl group, a 3,3,3-trifluoropropyl group, a 2,2,3,3,3-pentafluoropropyl group, a 2-fluorobutyl group, a 2-chlorobutyl group, a 2-bromobutyl group, a 4-fluorobutyl group, a 4-chlorobutyl group, a 4-bromobutyl group, a 4,4,4-trifluorobutyl group, a 2,2,3,3,4,4,4 -heptafluorobutyl group, a perfluorobutyl group, a 2-fluoropentyl group, a 2-chloropentyl group, a 2-bromopentyl group, a 5-fluoropentyl group, a 5-chloropentyl group, a 5-bromopentyl group, a perfluoropentyl group, a 2-fluorohexyl group, a 2-chlorohexyl group, a 2-bromohexyl group, a 6-fluorohexyl group, a 6-chlorohexyl group, a 6-bromohexyl group, a perfluorohexyl group, a 2-fluoroheptyl group, a 2-chloroheptyl group, a 2-bromoheptyl group, a 7-fluoroheptyl group, a 7-chloroheptyl group, a 7-bromoheptyl group, a perfluoroheptyl group, etc.

The lower alkoxy group is a linear or branched alkyloxy group having up to 6 carbon atoms. It includes, for example, a methoxy group, an ethoxy group, an n-propyloxy group, an i-propyloxy group, an n-butyloxy group, an i-butyloxy group, a sec-butyloxy group, a t-butyloxy group, an n-pentyloxy group, an i-pentyloxy group, a sec-pentyloxy group, a t-pentyloxy group, a 2-methylbutoxy group, an n-hexyloxy group, an i-hexyloxy group, a t-hexyloxy group, a sec-hexyloxy group, a 2-methylpentyloxy group, a 3-methylpentyloxy group, a 1-ethylbutyloxy group, a 2-ethylbutyloxy group, a 1,1-dimethylbutyloxy group, a 2,2-dimethylbutyloxy group, a 3,3-dimethylbutyloxy group, a 1-ethyl-1-methylpropyloxy group, etc. Preferred are a methoxy group, an ethoxy group, an n-propyloxy group, an i-propyloxy group, an n-butyloxy group, an i-butyloxy group, a sec-butyloxy group, a t-butyloxy group, etc.

The lower cycloalkyl group is a cycloalkyl group having from 3 to 7 carbon atoms, and preferably includes a cyclopropyl group, a cyclobutyl group, a cyclopentyl group, a cyclohexyl group, a cycloheptyl group, etc. More preferred are a cyclopropyl group, a cyclobutyl group, etc.

The lower alkoxy-lower alkyl group is a linear or branched alkyl group having up to 8 carbon atoms, as substituted with a linear or branched alkyloxy group having

up to 8 carbon atoms. For example, this includes a methoxymethyl group, a methoxyethyl group, a methoxypropyl group, a methoxybutyl group, a methoxypentyl group, a methoxyhexyl group, a methoxyheptyl group, a methoxyoctyl group, an ethoxymethyl group, an ethoxyethyl group, an ethoxybutyl group, an ethoxypentyl group, an ethoxyhexyl group, an ethoxyheptyl group, a ethoxyoctyl group, a propyloxymethyl group, a propyloxyethyl group, a propyloxypropyl group, a propyloxybutyl group, a propyloxypentyl group, an i-propyloxymethyl group, an i-propyloxyethyl group, an i-propyloxypropyl group, an i-propyloxybutyl group, an i-propyloxypentyl group, a butyloxymethyl group, a butyloxyethyl group, a butyloxypropyl group, a butyloxybutyl group, an i-butyloxymethyl group, an i-butyloxyethyl group, an i-butyloxypropyl group, an i-butyloxybutyl group, a sec-butyloxymethyl group, a sec-butyloxyethyl group, a sec-butyloxypropyl group, a sec-butyloxybutyl group, a t-butyloxymethyl group, a t-butyloxyethyl group, a t-butyloxypropyl group, a t-butyloxybutyl group, a pentyloxymethyl group, a pentyloxyethyl group, a pentyloxypropyl group, a pentyloxybutyl group, a hexyloxymethyl group, a hexyloxyethyl group, a hexyloxypropyl group, etc.

The tri-lower alkylsilyl-lower alkyl group is a lower alkyl group, such as that mentioned hereinabove, to which is bonded a trimethylsilyl group, a triethylsilyl group, a tripropylsilyl group or the like.

The lower alkylamino group is a linear or branched alkylamino group having up to 6 carbon atoms. This includes, for example, a methylamino group, an ethylamino group, an n-propylamino group, an i-propylamino group, an n-butylamino group, an i-butylamino group, a sec-butylamino group, a t-butylamino group, an n-pentylamino group, an i-pentylamino group, a sec-pentylamino group, a t-pentylamino group, a 2-methylbutylamino group, an n-hexylamino group, a 1-methylpentylamino group, a 2-methylpentylamino group, a 3-methylpentylamino group, a 4-methylpentylamino group, a 1-ethylbutylamino group, a 2-ethylbutylamino group, a 3-ethylbutylamino group, a 1,1-dimethylbutylamino group, a 2,2-dimethylbutylamino group, a 3,3-dimethylbutylamino group, a 1-ethyl-1-methylpropylamino group, etc. More preferred are a methylamino group, an ethylamino group, an n-propylamino group, an i-propylamino group, an n-butylamino group, an i-butylamino group, a sec-butylamino group, a t-butylamino group, etc.

The lower alkylthio group is a linear or branched alkylthio group having up to 6 carbon atoms. This includes, for example, a methylthio group, an ethylthio group, an n-propylthio group, an i-propylthio group, an n-butylthio group, an i-butylthio group, a sec-butylthio group, a t-butylthio group, an n-pentylthio group, an i-pentylthio group, a sec-pentylthio group, a t-pentylthio group, a 2-methylbutylthio group, an n-hexylthio group, an i-hexylthio group, a t-hexylthio group, a sec-hexylthio group, a 2-methylpentylthio group, a 3-methylpentylthio group, a 1-ethylbutylthio group, a 2-ethylbutylthio group, a 1,1-dimethylbutylthio group, a 2,2-dimethylbutylthio group, a 3,3-dimethylbutylthio group, a 1-ethyl-1-methylpropylthio group, etc. More preferred are a methylthio group, an ethylthio group, an n-propylthio group, an i-propylthio group, an n-butylthio group, an i-butylthio group, a sec-butylthio group, a t-butylthio group, etc.

The lower alkylthio-lower alkyl group is a linear or branched alkyl group having up to 6 carbon atoms, such as that mentioned hereinabove, as substituted with a linear or branched alkylthio group having up to 6 carbon atoms, such as that mentioned hereinabove.

The lower alkoxycarbonyl group is a linear or branched alkyloxycarbonyl group with a alkyl moiety having up to 6 carbon atoms. This includes, for example, a methoxycarbonyl group, an ethoxycarbonyl group, an n-propyloxycarbonyl group, an i-propyloxycarbonyl group, an n-butyloxycarbonyl group, an i-butyloxycarbonyl group, a sec-butyloxycarbonyl group, a t-butyloxycarbonyl group, an n-pentyloxycarbonyl group, an i-pentyloxycarbonyl group, a sec-pentyloxycarbonyl group, a t-pentyloxycarbonyl group, a 2-methylbutyloxycarbonyl group, an n-hexyloxycarbonyl group, an i-hexyloxycarbonyl group, a t-hexyloxycarbonyl group, a sec-hexyloxycarbonyl group, a 2-methylpentyloxycarbonyl group, a 3-methylpentyloxycarbonyl group, a 1-ethylbutyloxycarbonyl group, a 2-ethylbutyloxycarbonyl group, a 1,1-dimethylbutyloxycarbonyl group, a 2,2-dimethylbutyloxycarbonyl group, a 3,3-dimethylbutyloxycarbonyl group, a 1-ethyl-1-methylpropyloxycarbonyl group, etc. More preferred are a methoxycarbonyl group, an ethoxycarbonyl group, an n-propyloxycarbonyl group, an i-propyloxycarbonyl group, an n-butyloxycarbonyl group, an i-butyloxycarbonyl group, a sec-butyloxycarbonyl group, a t-butyloxycarbonyl group.

The lower alkanoyl group is a linear or branched alkylcarbonyl group having up to 6 carbon atoms. This includes, for example, a methylcarbonyl group, an ethylcarbonyl group, an n-propylcarbonyl group, an i-propylcarbonyl group, an n-butylcarbonyl group, an i-butylcarbonyl group, a sec-butylcarbonyl group, a t-butylcarbonyl group, an n-pentylcarbonyl group, an i-pentylcarbonyl group, a sec-pentylcarbonyl group, a t-pentylcarbonyl group, a 2-methylbutylcarbonyl group, an n-hexylcarbonyl group, an i-hexylcarbonyl group, a t-hexylcarbonyl group, a sec-hexylcarbonyl group, a 2-methylpentylcarbonyl group, a 3-methylpentylcarbonyl group, a 1-ethylbutylcarbonyl group, a 2-ethylbutylcarbonyl group, an 1,1-dimethylbutylcarbonyl group, a 2,2-dimethylbutylcarbonyl group, a 3,3-dimethylbutylcarbonyl group, a 1-ethyl-1-methylpropylcarbonyl group, etc. More preferred are a methylcarbonyl group, an ethylcarbonyl group, an n-propylcarbonyl group, an i-propylcarbonyl group, an n-butylcarbonyl group, an i-butylcarbonyl group, a sec-butylcarbonyl group, a t-butylcarbonyl group, etc.

The lower alkanesulfonyl group is a linear or branched alkanesulfonyl group having up to 6 carbon atoms. This includes, for example, a methanesulfonyl group, an ethanesulfonyl group, a 1-propanesulfonyl group, a 2-propanesulfonyl group, a 1-butanesulfonyl group, a 2-butanesulfonyl group, a 1,1-dimethylethanesulfonyl group, a 1-(2-methylpropane)sulfonyl group, a 1-pentanesulfonyl group, a 2-pentanesulfonyl group, a 3-pentanesulfonyl group, a 1-(3-methylbutane)sulfonyl group, a 1,1-dimethylpropanesulfonyl group, a 1-hexanesulfonyl group, a 2-hexanesulfonyl group, a 3-hexanesulfonyl group, a 1-(2-methylpentane)sulfonyl group, a 1-(3-methylpentane)sulfonyl group, a 1-(4-methylpentane)sulfonyl group, a 2-ethylbuthanesulfonyl group, a 3-ethylbutanesulfonyl group, a 1,1-dimethylbutanesulfonyl group, a 2,2-dimethylbutanesulfonyl group, a 3,3-dimethylbutanensulfonyl group, a 1-ethyl-1-methylpropanesulfonyl group, etc.

The aryl group includes, for example, a phenyl group, a naphthyl group, etc. The terminology "naphthyl" as referred to herein includes 1-naphthyl and 2-naphthyl. The benzene ring or the naphthalene ring in this group may optionally be substituted by one or more substituents selected from a

halogen atom, a lower alkyl group, a cyano group, a nitro group, a trifluoromethyl groups and the like, such as those mentioned hereinabove.

The arylsulfonyl group is a sulfonyl group, to which is bonded an aryl group such as that mentioned hereinabove, and includes, for example, a benzenesulfonyl group, a toluenesulfonyl group, a naphthalenesulfonyl group, etc.

The aryl-lower alkyl group is a lower alkyl group, such as that mentioned hereinabove, to which is bonded an aryl group such as that mentioned hereinabove, and includes, for example, a benzyl group, a 1-phenylethyl group, a 2-phenylethyl group, a phenylpropyl group, a phenylbutyl group, a phenylpentyl group, a phenylhexyl group, a naphthylmethyl group, a naphthylethyl group, a naphthylpropyl group, a naphthylbutyl group, a naphthylpentyl group, a naphthylhexyl group, etc.

The aryl-lower alkyloxy group includes, for example, a benzyloxy group, a 1-phenylethyloxy group, a 2-phenylethyloxy group, a phenylpropyloxy group, a phenylbutyloxy group, a phenylpentyloxy group, a phenylhexyloxy group, a naphthylmethyloxy group, a naphthylethyloxy group, a naphthylpropyloxy group, a naphthylbutyloxy group, a naphthylpentyloxy group, etc., in which the benzene ring or the naphthalene ring may optionally be substituted.

The arylsulfonyl-lower alkyl group is a lower alkyl group, such as that mentioned hereinabove, to which is bonded an arylsulfonyl group such as that mentioned hereinabove, and includes, for example, a benzenesulfonylmethyl group, a toluenesulfonylmethyl group, a naphthalenesulfonylmethyl group, etc.

The arylsulfonylamino group is an amino group to which is bonded an arylsulfonyl group such as that mentioned hereinabove, and this includes, for example, a benzenesulfonylamino group, a toluenesulfonylamino group, a naphthalenesulfonylamino group, etc.

The aryloxy group is an aryl group, such as that mentioned hereinabove, to which is bonded an oxygen atom, and this includes, for example, a phenoxy group, a 1-naphthoxy group, a 2-naphthoxy group, etc.

The arylcarbonyl group is a carbonyl group to which is bonded an aryl group such as that mentioned hereinabove, and this includes, for example, a phenylcarbonyl group, a naphthylcarbonyl group, etc.

The arylcarbonylamino group is an amino group to which is bonded an arylcarbonyl group such as that mentioned hereinabove, and this includes, for example, a phenylcarbonylamino group, a naphthylcarbonylamino group, etc.

The aryl-lower alkenyl group is an alkenyl group having 6 or less carbon atoms, which is substituted by an aryl group such as that mentioned hereinabove, and this includes, for example, a phenylethenyl group, a naphthylethenyl group, etc.

The heterocyclic group includes, for example, a pyridyl group, a quinolyl group, an isoquinolyl group, a thiazolyl group, a thiadiazolyl group, a benzofuranyl group, a dibenzofuranyl group, a thianaphthalenyl group, a 1H-1,2,3-triazolyl group, a 1,2,4-triazolyl group, a tetrazolyl group, a furyl group, a thienyl group, a pyrrolyl group, an imidazolyl group, a pyrimidinyl group, an indolyl group, a benzimidazolyl group, etc. The heterocyclic group may optionally be substituted by one or more substituents of halogen atoms and lower alkyl groups, such as those mentioned hereinabove, and the substituted heterocyclic group of that type includes, for example, a haloisoquinolyl group, a methylisoquinolyl group, etc.

The heterocyclic lower alkyl group means a lower alkyl group, such as that mentioned hereinabove, as substituted by a heterocyclic group, such as that mentioned hereinabove. This includes, for example, a pyridylmethyl group. The halo-heterocyclic lower alkyl group is a heterocyclic lower alkyl group, such as that mentioned hereinabove, in which the heterocyclic moiety is substituted with one or more halogens.

The heterocyclic lower alkylamino group is an amino group as substituted with a heterocyclic lower alkyl group, such as that mentioned hereinabove, and this includes, for example, a pyridylmethylamino group, etc. The heterocyclic lower alkylcarbamoyl group is a carbamoyl group as substituted with a heterocyclic lower alkyl group, such as that mentioned hereinabove, and this includes, for example, a pyridylmethylcarbamoyl group, etc.

The terminology "pyridyl" as referred to herein includes 2-pyridyl, 3-pyridyl and 4-pyridyl, for which the bonding position is not specifically defined. The same shall apply to the other heterocyclic groups as referred to herein, or that is, the bonding positions of the heterocyclic groups as referred to herein are not specifically defined.

The lower alkylenedioxybenzyl group includes, for example, a methylenedioxybenzyl group, an ethylenedioxybenzyl group, a propylenedioxybenzyl group, etc.

A suitable heterocyclic group used herein means a saturated or unsaturated mono- or polycyclic hetero ring containing at least one hetero atom such as an oxygen atom, a sulfur atom, a nitrogen atom, etc.

Preferable examples thereof include the following heterocyclic groups:

- 7- to 12-membered, preferably 9- or 10-membered unsaturated condensed heterocyclic group (preferably bicyclic group) having 1 to 5 nitrogen atoms, such as indolyl, isoindolyl, indolidinyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, tetrazolopyridyl, tetrazolopyridazinyl (e.g. tetrazolo[1,5-b]pyridazinyl, etc.), dihydrotriazolopyridazinyl, or the like;
- 7- to 12-membered, preferably 9- or 10-membered unsaturated condensed heterocyclic group (preferably bicyclic group) having 1 to 3 sulfur atoms or S,S-dioxide thereof, such as dithianaphthalenyl (e.g. 4H-1,3-dithianaphthalenyl, 1,4-dithianaphthalenyl, etc.), benzothiophenyl or S,S-dioxide thereof (e.g. benzo[a]thiophenyl or S,S-dioxide thereof, benzo[b]thiophenyl or S,S-dioxide thereof, etc.), or the like;
- 3- to 8-membered, preferably 5- or 6-membered unsaturated hetero monocyclic group having 1 to 4 nitrogen atoms, such as pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl and its N-oxide, pyrimidyl, pyrazinyl, pyridazinyl, triazolyl (e.g. 4H-1,2,3-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc.), dihydrotriazinyl (e.g. 4,5-dihydro-1,2,4-triazinyl, 2,5-dihydro-1,2,4-triazinyl, etc.), or the like;
- 3- to 8-membered, preferably 5- or 6-membered saturated hetero monocyclic group having 1 to 4 nitrogen atoms, such as azetydinyl, pyrrolidinyl, imidazolydinyl, piperidinyl, pyrazolydinyl, piperadinyl, or the like;
- 7- to 12-membered, preferably 9- or 10-membered unsaturated condensed heterocyclic group (preferably bicyclic group) having 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, such as benzooxazolyl, benzooxadiazolyl, or the like;
- 3- to 8-membered, preferably 5- or 6-membered unsaturated hetero monocyclic group having 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, such as oxazolyl, isooxazolyl, oxadiazolyl (e.g. 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, etc.), or the like;

3- to 8-membered, preferably 5- or 6-membered saturated hetero monocyclic group having 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, such as morpholinyl or the like;

7- to 12-membered, preferably 9- or 10-membered unsaturated condensed heterocyclic group (preferably bicyclic group) having 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms, such as benzothiazolyl, benzothiadiazolyl, or the like;

3- to 8-membered, preferably 5- or 6-membered unsaturated hetero monocyclic group having 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms, such as thiazolyl, 1,2-thiazolyl, thiadiazolyl (e.g. 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,2,3-thiadiazolyl, etc.), or the like;

3- to 8-membered, preferably 5- or 6-membered saturated hetero monocyclic group having 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms, such as thiazolydinyl;

3- to 8-membered, preferably 5- or 6-membered unsaturated hetero monocyclic group having one sulfur atom, such as thienyl or the like; etc.

Suitable "esterified carboxyl groups" are exemplified below.

The ester portion of the esterified carboxyl group suitably include a lower alkyl ester, such as methyl ester, ethyl ester, propyl ester, isopropyl ester, butyl ester, isobutyl ester, tertiary butyl ester, pentyl ester, or hexyl ester, which may have at least one appropriate substituent. Examples of the lower alkyl ester include lower alkanoyloxy(lower)alkyl ester, such as acetoxymethyl ester, propionyloxymethyl ester, butyryloxymethyl ester, valeryloxymethyl ester, pivaloyloxymethyl ester, hexanoyloxy methyl ester, 1-(or 2-)acetoxyethyl ester, 1-(2-, or 3-)acetoxypropyl ester, 1-(2-, 3- or 4-)acetoxybutyl ester, 1-(or 2-)propionyloxyethyl ester, 1-(2-, or 3-)propionyloxypropyl ester, 1-(or 2-)butyryloxyethyl ester, 1(or 2 -)isobutyryloxyethyl ester, 1-(or 2-)pivaloyloxyethyl ester, 1-(or 2-)hexanoyloxyethyl ester, isobutyryloxymethyl ester, 2-ethylbutyryloxymethyl ester, 3,3-dimethylbutyryloxymethyl ester, or 1-(or 2-)pentanoyloxyethyl ester, lower alkanesulfonyl(lower) alkyl ester, such as 2-mesylethyl ester, mono(di, or tri)halo (lower)alkyl ester, such as 2-iodoethyl ester, 2,2,2-trichloroethyl ester, lower alkoxycarbonyloxy(lower)alkyl ester, such as methoxycarbonyloxymethyl ester, ethoxycarbonyloxymethyl ester, propoxycarbonyloxymethyl ester, tertiary-butoxycarbonyloxymethyl ester, 1-(or 2-)methoxycarbonyloxyethyl ester, 1-(or 2-)ethoxycarbonyloxyethyl ester, or 1-(or 2-)isopropoxycarbonyloxyethyl ester, phthalizilidene (lower)alkyl ester or (5-lower alkyl-2-oxo-1,3-dioxol-4-yl) (lower)alkyl ester, such as (5-methyl-2-oxo-1,3-dioxol-4-yl) methyl ester, (5-ethyl-2-oxo-1,3-dioxol-4-yl)methyl ester, or (5-propyl-2-oxo-1,3-dioxol-4-yl)ethyl ester, lower alkenyl ester, such as vinyl ester or allyl ester, lower alkynyl ester, such as ethynyl ester or propinyl ester, ar(lower)alkyl ester which may have at least one appropriate substituent, such as benzyl ester, 4-methoxybenzyl ester, 4-nitrobenzyl ester, phenethyl ester, trityl ester, benzhydryl ester, bis (methoxyphenyl)methyl ester, 3,4-dimethoxybenzyl ester, or 4-hydroxy-3,5-di-tertiary-butylbenzyl ester, aryl ester which may have at least one appropriate substituent, such as phenyl ester, 4-chlorophenyl ester, tolyl ester, tertiary-butylphenyl ester, xylyl ester, mesityl ester, or cumenyl ester, phthalidyl ester, etc.

Preferable examples of a carboxyl groups protected by esterification include lower alkoxycarbonyl and phenyl(or nitrophenyl) (C_1–C_4)alkoxycarbonyl. Most preferred are methoxycarbonyl, ethoxycarbonyl, and benzyloxycarbonyl.

Suitable amidated carboxyl groups include the following:

a carbamoyl group;

a mono- or di-lower alkyl carbamoyl group (as a lower alkyl group, those as described above can be used), such as methylcarbamoyl, dimethylcarbamoyl, isopropylcarbamoyl, n-butylcarbamoyl, t-butylcarbamoyl, N-methyl-N-(pyridylmethyl) carbamoyl, or the like;

an aryl(lower alkyl)carbamoyl (as an aryl group and a lower alkyl group, those as described above can be used), such as benzylcarbamoyl, 3,4-methylenedioxybenzylcarbamoyl, diaminobenzylcarbamoyl, or phenethylcarbamoyl;

a cyclo(lower alkyl)carbamoyl having 3 to 7 carbon atoms (as a cyclo lower alkyl group, those as described above can be used), such as cyclopropylcarbamoyl, cyclobutylcarbamoyl, cyclopentylcarbamoyl, cyclohexylcarbamoyl or the like;

an arylcabamoyl group (as an aryl group, those as described above can be used), such as phenylcarbamoyl, naphthylcarbamoyl, or the like;

a heterocyclic carbamoyl group (as a heterocyclic group, those as described above can be used), such as thiazolylcarbamoyl, thiadiazolylcarbamoyl, pyridylcarbamoyl, triazolylcarbamoyl, tetrazolylcarbamoyl, N-methyl-N-pyridinecarbamoyl, morpholinocarbamoyl, or the like;

a heterocyclic(lower alkyl)carbamoyl group (as a heterocyclic lower alkyl group, those as described above can be used), such as morpholinoethylcarbamoyl, pyridylmethylcarbamoyl, methylenedioxybenzylcarbamoyl, or the like;

an N-di-substituted carbamoyl group containing nitrogen as a member of a nitrogen-containing heterocyclic ring, such as morpholinocarbonyl, thiomorpholinocarbonyl, 1-perhydroazepinylcarbonyl, 1,1-dioxothiazolydinecarbonyl, piperidinocarbonyl, 1-piperazinylcarbonyl, 4-(2-hydroxyethyl)-1-piperazinylcarbonyl, 4-methyl-1-piperazinylcarbonyl, carboxypyrrolidinocarbonyl, or the like;

a substituted sulfonylcarbomoyl group, etc.

The substituent for the substituted sulfonyl-carbamoyl group includes the above-described groups such as the alkyl group having carbon atoms up to 8, the halo lower alkyl group, the aryl lower alkyl group, the hydroxy-lower alkyl group, the tri(lower alkyl)silyl(lower alkyl) group, the lower alkoxy-lower alkyl group, the lower alkylthio-lower alkyl group, the heterocyclic group, the aryl group, and the like. The aryl group may be substituted by a halogen atom, a lower alkyl group a halo lower alkyl group, a lower alkoxy group, a nitro group, or the like. Specific examples of the substituted sulfonylcarbamoyl group include naphthylsulfonylcarbamoyl, benzenesulfonylcarbamoyl, nitrobenzenesulfonylcarbamoyl, trihalobenzenesulfonylcarbamoyl, lower alkoxybenzenesulfonylcarbamoyl, halobenzenesulfonylcarbamoyl, mono- or di-(lower alkyl) benzenesulfonylcarbamoyl, alkanesulfonylcarbamoyl having 1 to 8 carbon atoms, such as t-butylsulfonylcarbamoyl, butylsulfonylcarbamoyl, propylsulfonylcarbamoyl, isopropylsulfonylcarbamoyl, methylsulfonylcarbamoyl, octylsulfonylcarbamoyl, pentylsulfonylcarbamoyl, isopentylsulfonylcarbamoyl, hexylsulfonylcarbamoyl, or the like, trihalo(lower)alkylsulfonylcarbamoyl, phenyl (lower)alkylsulfonylcarbamoyl, tri(lower) alkylsulfonylcarbamoyl, lower alkylthio(lower)

alkylsulfonylcarbamoyl, lower alkoxy(lower) alkylsulfonylcarbamoyl, quinolinesulfonylcarbamoyl, or the like.

Suitable acyl groups include aliphatic acyl, aromatic acyl, heterocyclic acyl, and aliphatic acyl substituted with an aromatic group or a heterocyclic group, which are derived from carboxylic acid, carbonic acid, sulfonic acid, carbamic acid, and the like.

Examples of the aliphatic acyl include saturated or unsaturated non-cyclic or cyclic ones, for example, alkanoyl such as lower alkanoyl (e.g. formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, etc.), alkylsulfonyl such as lower alkyl sulfonyl (e.g. mesyl, ethylsulfonyl, propylsulfonyl, isopropylsulfonyl, butylsulfonyl, isobutylsulfonyl, pentylsulfonyl, hexylsulfonyl, etc.), carbamoyl, N-alkylcarbamoyl (e.g. methylcarbamoyl, ethylcarbamoyl, etc.), alkoxycarbonyl such as lower alkoxy carbonyl (e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, tertiary-butoxycarbonyl, etc.), alkenyloxycarbonyl such as lower alkenyloxycarbonyl (e.g. vinyloxycarbonyl, allyloxycarbonyl, etc.), alkenoyl such as lower alkenoyl (e.g. acryloyl, methacryloyl, chlotonoyl, etc.), cycloalkanecarbonyl such as cyclo(lower)alkanecarbonyl (e.g. cyclopropanecarbonyl, cyclopentanecarbonyl, cyclohexanecarbonyl, etc.) and the like.

Examples of the aromatic acyl include C_6–C_{10} aroyl (e.g. benzoyl, toluoyl, xyloyl, etc.), N-(C_6–C_{10})arylcarbamoyl (e.g. N-phenylcarbamoyl, N-tolylcarbamoyl, N-naphthylcarbamoyl, etc.), C_6–C_{10} arenesulfonyl (e.g. benzenesulfonyl, tosyl, etc.), and the like.

Examples of the heterocyclic acyl include heterocyclic carbonyl, heherocyclic (lower)alkanoyl (e.g. heterocyclic acetyl, heterocyclic propanoyl, heterocyclic butanoyl, heterocyclic pentanoyl, heterocyclic hexanoyl, etc.), heterocyclic(lower)alkenoyl (e.g. heterocyclic propenoyl, heterocyclic butenoyl, heterocyclic pentenoyl, heterocyclic hexenoyl, etc.) heterocyclic glyoxyloyl, heterocyclic sulfinyl, heterocyclic sulfonyl, etc.

The aromatic group-bound aliphatic acyl includes aralkoxycarbonyl such as phenyl(lower)alkoxycarbonyl (e.g. benzyloxycarbonyl, phenethyloxycarbonyl, etc.).

These acyl groups may be substituted with one or more appropriate substituent, such as a nitro group. An example thereof is nitroaralkoxycarbonyl (e.g. nitrobenzyloxycarbonyl, etc.).

Preferred salts of the benzimidazole derivatives of the present invention are non-toxic, ordinary pharmaceutically acceptable salts thereof. For example, mentioned are salts of the derivatives with bases as well as acid-addition salts of the derivatives, which include, for example, salts thereof with inorganic bases, such as salts with alkali metals (e.g., sodium, potassium); salts with alkaline earth metals (e.g., calcium, magnesium); ammonium salts; salts with organic amines (e.g., triethylamine, pyridine, picoline, ethanolamine, triethanolamine, dicyclohexylamine, N,N'-dibenzylethylenediamine); salts with inorganic acids (e.g., hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid); salts with organic carboxylic acids (e.g., formic acid, acetic acid, trifluoroacetic acid, maleic acid, tartaric acid); salts with sulfonic acids (e.g., methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid); salts with basic or acidic amino acids (e.g., arginine, aspartic acid, glutamic acid), etc.

The compounds of the invention could contain one or more chiral centers, therefore they could be enantiomers or diastereomers. Few of the compounds containing alkenyl group could also be cis- or trans-isomers. In both cases, each of such isomers as well as the mixture thereof are within the scope of this invention.

The compounds of the invention can also exist as tautomers, and individual of such tautmers and the mixture thereof are within the scope of this invention.

The compounds of the invention and their salts can be solvate, which are also within the invention. The solvent for the solvate is preferably water or ethanol.

Specific examples of benzimidazole derivatives of formula (IX) include 6-benzenesulfonylcarbamoyl-1-(2-chlorobenzyl)-2-methylbenzimidazole, 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-ethylbenzimidazole, 5-benzenesulfonylcarbamoyl-1-(2-chlorobenzyl)-2-methylbenzimidazole, 5-(4-chlorobenzenesulfonylcarbamoyl)-1-(2-chlorobenzyl)-2-methylbenzimidazole, 1-(2-chlorobenzyl)-2-methyl-5-(2-naphthalenesulfonylcarbamoyl)benzimidazole, 1-(2-chlorobenzyl)-6-methanesulfonylcarbamoyl-2-methylbenzimidazole, 6-(1-butanesulfonylcarbamoyl)-1-(2-chlorobenzyl)-2-methylbenzimidazole, 1-(2-chlorobenzyl)-2-methyl-6-(1-octanesulfonylcarbamoyl)benzimidazole, 1-(2-chlorobenzyl)-2-methyl-6-(2-propanesufonylcarbamoyl)benzimidazole, 1-(biphenyl-4-ylmethyl)-6-(1-butanesulfonylcarbamoyl)-2-methylbenzimidazole, 6-(1-butanesulfonylcarbamoyl)-1-(2,4-dichlorobenzyl)-2 -methylbenzimidazole, 1-(biphenyl-4-ylmethyl)-6-(1-butanesulfonylcarbamoyl)-2-ethylbenzimidazole, 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-trifluoromethylbenzimidazole, 5-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-trifluoromethylbenzimidazole, 6-benzenesulfonylcarbamoyl-2-cyclopropyl-1-(2-fluorobenzyl)benzimidazole, N-benzenesulfonyl-3-[1-(2-chlorobenzyl)-2-methylbenzimidazol-6-yl]acrylamide, N-benzenesulfonyl-2-[1-(2-chlorobenzyl)-2-methylbenzimidazol-6-yl]acetamide, 1-(2-chlorobenzyl)-2-methyl-6-(2-naphthalenesulfonylcarbamoyl)benzimidazole, 1-(2-chlorobenzyl)-2-methyl-6-(1-naphthalenesulfonylcarbamoyl)benzimidazole, 6-(4-chlorobenzenesulfonylcarbamoyl)-1-(2-chlorobenzyl)-2-methylbenzimidazole, 6-(3-chlorobenzenesulfonylcarbamoyl)-1-(2-chlorobenzyl)-2-methylbenzimidazole, 5-benzenesulfonylcarbamoyl-2-benzyl-1-(2-chlorobenzyl)benzimidazole, 6-benzenesulfonylcarbamoyl-2-benzyl-1-(2-chlorobenzyl)benzimidazole, 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-methylbenzimidazole, 1-(2-chlorobenzyl)-2-methyl-6-trifluoromethanesulfonylcarbamoylbenzimidazole, 6-benzenesulfonylcarbamoyl-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole, 1-(2-chlorobenzyl)-6-(4-methoxybenzenesulfonylcarbamoyl)-2-methylbenzimidazole, 1-(2-chlorobenzyl)-2-methyl-6-(α-toluenesulfonylcarbamoyl)benzimidazole, 1-(2-chlorobenzyl)-6-(2,5-dimethylbenzenesulfonylcarbamoyl)-2-methylbenzimidazole, 1-(2-chlorobenzyl)-2-methyl-6-(4-nitrobenzenesulfonylcarbamoyl)benzimidazole, 1-(2-chlorobenzyl)-2-methyl-6-[4-(trifluoromethyl)benzenesulfonylcarbamoyl]benzimidazole, 6-(2-chlorobenzenesulfonylcarbamoyl)-1-(2-chlorobenzyl)-2-methylbenzimidazole, 6-benzenesulfonylcarbamoyl-2-benzyl-1-(2,4-dichlorobenzyl)benzimidazole, 5-benzenesulfonylcarbamoyl-2-benzyl-1-(2,4-dichlorobenzyl)benzimidazole, 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-hydroxybenzimidazole, 6-benzenesulfonylcarbamoyl-1-

(biphenyl-4-ylmethyl)-2-mercaptobenzimidazole, 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-methoxybenzimidazole, 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-carboxybenzimidazole, 6-benzenesulfonylcarbamoyl- 1-(biphenyl-4-ylmethyl)-2-methylaminobenzimidazole, 2-amino-6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl) benzimidazole, 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-n-propylbenzimidazole, 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-n-heptylbenzimidazole, 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-chloromethylbenzimidazole, 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-methoxymethylbenzimidazole, 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-i-propylbenzimidazole, 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-methylthiobenzimidazole, 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-ethylthiobenzimidazole, 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-n-propylthiobenzimidazole, 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-n-hexylthiobenzimidazole, 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)benzimidazole, 6-benzenesulfonylcarbamoyl-1-(2,4-difluorobenzyl)-2-methylbenzimidazole, 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-phenylbenzimidazole, 6-benzenesulfonylcarbamoyl-2-methyl-1-(2-nitrobenzyl) benzimidazole, 6-benzenesulfonylcarbamoyl-2-methyl-1-benzylbenzimidazole, 6-benzenesulfonylcarbamoyl-2-methyl-1-(4-nitrobenzyl)benzimidazole, 6-benzenesulfonylcarbamoyl-1-(4-benzyloxybenzyl)-2-methylbenzimidazole, 6-benzenesulfonylaminomethyl-1-(2-chlorobenzyl)-2-methylbenzimidazole, N-benzenesulfonyl-3-[1-(2-chlorobenzyl)-2-methylbenzimidazol-6-yl]propionamide, 6-benzenesulfonylcarbamoyl-2-methyl-1-[4-(1,2,3-thiadiazol-4-yl)benzyl]benzimidazole, 1-(2-chlorobenzyl)-2-methyl-6-(8-quinolinesulfonylcarbamoyl)benzimidazole, 6-(4-t-butylbenzenesulfonylcarbamoyl)-1-(2-chlorobenzyl)-2-methylbenzimidazole, 6-benzenesulfonylcarbamoyl-2-methyl-1-[4-(trifluoromethyl)benzyl]benzimidazole, 5-benzenesulfonylcarbamoyl-2-methylbenzimidaozle, 1-(biphenyl-4-ylmethyl)-6-(1-butanesulfonylcarbamoyl)-2-methoxymethylbenzimidazole, 1-(4-benzyloxybenzyl)-6-(1-butanesulfonylcarbamoyl)-2-methoxymethylbenzimidazole, 6-(1-butanesulfonylcarbamoyl)-1-(2,4 -dichlorobenzyl)-2-methoxymethylbenzimidazole, 1-(2-chlorobenzyl)-2-methyl-6-(1-propanesulfonylcarbamoyl)benzimidazole, 6-ethanesulfonylcarbamoyl-1-(2-chlorobenzyl)-2-methylbenzimidazole, 6-(propanesultam-1-ylcarbonyl)-1-(2-chlorobenzyl)-2-methylbenzimidazole, 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-cyclopropylbenzimidazole, 1-(2-chlorobenzyl)-2-methyl-6-(1-pentanesulfonylcarbamoyl)benzimidazole, 1-(2-chlorobenzyl)-2-methyl-6-[(3-methylbutane) sulfonylcarbamoyl]benzimidazole, 1-(2-chlorobenzyl)-6-(1-hexanesulfonylcarbamoyl)-2-methylbenzimidazole, 7-(1-butanesulfonylcarbamoyl)-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole, 1-(2-chlorobenzyl)-2-methyl-6-[1-[3-(trimethylsilyl)propane]sulfonylcarbamoyl] benzimidazole, 4-(1-butanesulfonylcarbamoyl)-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole, 1-(4-benzyloxybenzyl)-6-(1-butanesulfonylcarbamoyl)-2-methylbenzimidazole, 6-(1-butanesulfonylcarbamoyl)-1-[(2'-cyanobiphenyl-4-yl)methyl]-2-methylbenzimidazole, 6-(1-ethanesulfonyl-carbamoyl)-1-[(2'-fluorobiphenyl-4-yl) methyl]-2-methylbenzimidazole, 6-(1-butanesulfonylcarbamoyl)-1-[(3-fluorobiphenyl-4-yl) methyl]-2-methylbenzimidazole, 1-(2-chlorobenzyl)-6-[(2-methoxyethane)sulfonylcarbamoyl]-2-methylbenzimidazole, 1-(2-chlorobenzyl)-6-(1-hexanesulfonylcarbamoyl)-2-methylbenzimidazole, 1-(2,4-dichlorobenzyl)-2-methyl(1-pentanesulfonylcarbamoyl) benzimidazole, 1-(biphenyl-4-ylmethyl)-2-ethyl-6-[1-[3-(methylthio)propane]sulfonylcarbamoyl]benzimidazole, 1-(4-biphenylmethyl)-2-ethyl-6-(1-pentanesulfonylcarbamoyl)benzimidazole, 6-(1-butanesulfonylcarbamoyl)-1-(2,4-dichlorobenzyl)-2-ethylbenzimidazole, 1-(4-biphenylmethyl)-2-ethyl-6-[1-(3-methyl)butanesulfonylcarbamoyl]benzimidazole, 5-(1-butanesulfonylcarbamoyl)-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole, 1-(4-biphenylmethyl)-5-(1-butanesulfonylcarbamoyl)-2-ethylbenzimidazole, 1-(4-biphenylmethyl)-2-ethyl-6-(2-methoxyethanesulfonylcarbamoyl)benzimidazole, 6-(1-butanesulfonylcarbamoyl)-2-ethyl-1-[4-(4-fluorobenzyloxy)benzyl]benzimidazole, 6-(1-butanesulfonylcarbamoyl)-1-[4-(3,4-dichlorobenzyloxy) benzyl]-2-ethylbenzimidazole, 6-(1-butanesulfonylcarbamoyl)-1-[sec-(2,4-dichlorophenethyl)]-2-methylbenzimidazole, 6-(1-butanesulfonylcarbamoyl)-1-[4-(2-pyridyl)benzyl]-2-methylbenzimidazole, 6-(1-butanesulfonylcarbamoyl)-1-(2,4-dichlorobenzyl)-2,4-dimethylbenzimidazole, 6-(1-butanesulfonylcarbamoyl)-2-methyl-1-(4-phenoxybenzyl)benzimidazole, 6-(butanesulfonylcarbamoyl)-2-methyl-1-(2-pyridylmethyl) benzimidazole, 1-[(4-benzoylamino)benzyl]-6-(1-butanesulfonylcarbamoyl)-2-methylbenzimidazole, 6-(1-butanesulfonylcarbamoyl)-2-methyl-[4-(2-phenylethyl) benzyl]benzimidazole, 1-[(4-benzoyl)benzyl]-6-(1-butanesulfonylcarbamoyl)-2-methylbenzimidazole, 6-(1-butanesulfonylcarbamoyl)-2-methyl-[4-(2-phenylethenyl) benzyl]benzimidazole, 1-(dibenzofuran-2-ylmethyl)-6-(1-butanesulfonylcarbamoyl)-2-methylbenzimidazole, 6-(1-butanesulfonylcarbamoyl)-1-(2,4-dichlorobenzyl)-2-hydroxybenzimidazole, 6-(1-butanesulfonylcarbamoyl)-2-methyl-1-(2-quinolylmethyl)benzimidazole, and 6-(1-butanesulfonylcarbamoyl)-2-methyl-1-[3-(4-bromoisoquinolyl)methyl]benzimidazole, etc.

Specific examples of compounds of formula (X) include 1-(2-cyanobenzyl)-6-ethoxycarbonyl-2-n-propylbenzimidazole, 6-ethoxycarbonyl-2-N-propyl-1-(2-pyridylmethyl)benzimidazole, 6-ethoxycarbonyl-1-methyl-2-n-propylbenzimidazole, 1-n-butyl-6-ethoxycarbonyl-2-n-propylbenzimidazole, 1-(biphenyl-4-ylmethyl)-6-ethoxycarbonyl-2-methylbenzimidazole, 6-ethoxycarbonyl-1-(2-methoxybenzyl)-2-methylbenzimidazole, 6-ethoxycarbonyl-1-(4-methoxybenzyl)-2-methylbenzimidazole, 1-[2-(benzenesulfonylmethyl) benzyl]-6-ethoxycarbonyl-2-methylbenzimidazole, 1-(2-cyanobenzyl)-6-(2-cyanobenzyloxycarbonyl)-2-methylbenzimidazole, 1-(biphenyl-2-ylmethyl)-6-ethoxycarbonyl-2-methyl-benzimidazole, 6-ethoxycarbonyl-2-methyl-1-(2-naphthylmethyl) benzimidazole, 1-(biphenyl-4-ylmethyl)-6-ethoxycarbonyl-2-ethylbenzimidazole, 6-ethoxycarbonyl-2-n-propyl-1-i-propylbenzimidazole, 2-benzyl-6-ethoxycarbonyl-1-methylbenzimidazole, 6-carboxy-1-methyl-2-n-propylbenzimidazole, 6-carboxy-2-n-propyl-1-i-propylbenzimidazole, 1-n-butyl-6-carboxy-2-n-propylbenzimidazole, 6 -carboxy-2-methyl-1-(2-nitrobenzyl)benzimidazole, 1-(biphenyl-4-ylmethyl)-6-carboxy-2-methylbenzimidazole, 6-carboxy-1-(2-methoxybenzyl)-2-methylbenzimidazole, 6-carboxy-1-(4-

methoxybenzyl)-2-methylbenzimidazole, 6-carboxy-2-methyl-1-[2-(benzenesulfonylmethyl)benzyl] benzimidazole, 6-carboxy-1-(2-cyanobenzyl)-2-methylbenzimidazole, 6-carboxy-1-(biphenyl-2-ylmethyl)-2-methylbenzimidazole, 6-carboxy-2-methyl-1-(2-naphthylmethyl)benzimidazole, 1-(biphenyl-4-ylmethyl)-6-carboxy-2-ethylbenzimidazole, 5-carboxy-2-methyl-1-(2-nitrobenzyl)benzimidazole, 1-(biphenyl-4-ylmethyl)-6-carboxy-2-trifluoromethylbenzimidazole, 1-(biphenyl-4-ylmethyl)-5-carboxy-2-trifluoromethylbenzimidazole, 5-ethoxycarbonyl-2-methylbenzimidazole, 2-benzyl-5-ethoxycarbonylbenzimidazole, 6-ethoxycarbonyl-2-methyl-1-(2-nitrobenzyl)benzimidazole, 5-ethoxycarbonyl-2-methyl-1-(2-nitrobenzyl)benzimidazole, 5-ethoxycarbonyl-2-trifluoromethylbenzimidazole, 1-(biphenyl-4-ylmethyl)-6-ethoxycarbonyl-2-trifluoromethylbenzimidazole, 1-(biphenyl-4-ylmethyl)-5-ethoxycarbonyl-2-trifluoromethylbenzimidazole, 1-methyl-2-n-propyl-6-[(2-pyridylmethyl)carbamoyl]benzimidazole, 2-n-propyl-1-i-propyl-6-[(2-pyridylmethyl)carbamoyl]benzimidazole, 1-n-butyl-2-n-propyl-6-[(2-pyridylmethyl)carbamoyl] benzimidazole, 2-benzyl-1-methyl-6- (2-pyridylmethyl) carbamoyl]benzimidazole, 1-(2-methoxybenzyl)-2-methyl-6-[(2-pyridylmethyl)carbamoyl]benzimidazole, 1-(4-methoxybenzyl)-2-methyl-6-[(2-pyridylmethyl)carbamoyl] benzimidazole, 1-[2-(benzenesulfonylmethyl)benzyl]-2-methyl-6-[(2-pyridylmethyl)carbamoyl]benzimidazole, 1-(2-cyanobenzyl)-2-methyl-6-[(2-pyridylmethyl) carbamoyl]benzimidazole, 1-(biphenyl-2-ylmethyl)-2-methyl-6-[(2-pyridylmethyl)carbamoyl]benzimidazole, 2-methyl-1-(2-naphthylmethyl)-6-[(2-pyridylmethyl) carbamoyl]benzimidazole, 1-(biphenyl-4-ylmethyl)-2-ethyl-6-[(2-pyridylmethyl)carbamoyl]benzimidazole, 2-methyl-1-(2-nitrobenzyl)-6-[(2-pyridylmethyl) carbamoyl]benzimidazole, 2-methyl-1-(2-nitrobenzyl)-5-[(2-pyridylmethyl)carbamoyl]benzimidazole, 1-(biphenyl-4-ylmethyl)-2-methyl-6-[(2-pyridylmethyl)carbamoyl] benzimidazole, 1-(4-benzyloxybenzyl)-2-methyl-6-[(2-pyridylmethyl)carbamoyl]benzimidazole, 2-methyl-1-(3,4-methylenedioxybenzyl)-6-[(2-pyridylmethyl)carbamoyl] benzimidazole, 2-methyl-6-[(2-pyridylmethyl)carbamoyl]-1-[4-(1,2,3-thiadiazol-4-yl)benzyl]benzimidazole, 2-methyl-5-[(2-pyridylmethyl)carbamoyl]benzimidazole, 1-benzenesulfonyl-2-methyl-6-[(2-pyridylmethyl) carbamoyl]benzimidazole, 1-benzenesulfonyl-2-methyl-5-[(2-pyridylmethyl)carbamoyl]benzimidazole, 2-methyl-1-(4-nitrobenzyl)-6-[(2-pyridylmethyl)carbamoyl] benzimidazole, 2-methyl-1-(4-nitrobenzyl)-5-[(2-pyridylmethyl)carbamoyl]benzimidazole, 2-methyl-1-(2-phenylethyl)-6-[(2-pyridylmethyl)carbamoyl] benzimidazole, 2-methyl-1-(2-phenylethyl)-5-[(2-pyridylmethyl)carbamoyl]benzimidazole, 1-(4-aminobenzyl)-2-methyl-6-[(2-pyridylmethyl)carbamoyl] benzimidazole, 1-(4-aminobenzyl)-2-methyl-5-[(2-pyridylmethyl)carbamoyl]benzimidazole, 1-[4-(benzenesulfonylamino)benzyl]-2-methyl-6-[(2-pyridylmethyl)carbamoyl]benzimidazole, 1-(biphenyl-4-ylmethyl)-2-methyl-6-[(2-pyridylmethyl)aminomethyl] benzimidazole, 2-benzyl-6-carboxy-1-methylbenzimidazole, 4-ethoxycarbonyl-2-methylbenzimidazole, 1-(4-benzyloxybenzyl)-6-ethoxycarbonyl-2-methylbenzimidazole, 1-(4-benzyloxybenzyl)-6-carboxy-2-methylbenzimidazole, 6-ethoxycarbonyl-1-[(2'-cyanobiphenyl-4-yl)methyl]-2-methylbenzimidazole, 6-carboxy-1-[(2'-cyanobiphenyl-4-yl)methyl]-2-methylbenzimidazole, 6-ethoxycarbonyl-1-[(2'-fluorobiphenyl-4-yl)methyl]-2-methylbenzimidazole, 6-carboxy-1-[(2'-fluorobiphenyl-4-yl)methyl]-2-methylbenzimidazole, 6-ethoxycarbonyl-1-[(3-fluorobiphenyl-4-yl)methyl]-2-methylbenzimidazole, 6-carboxy-1-[(3-fluorobiphenyl-4-yl)methyl]-2-methylbenzimidazole, 1-(4-biphenylmethyl)-5-ethoxycarbonyl-2-ethylbenzimidazole, 1-(4-biphenylmethyl)-5-carboxy-2-ethylbenzimidazole, 6-ethoxycarbonyl-2-ethyl-1-[4-(4-fluorobenzyloxy)benzyl] benzimidazole, 6-carboxy-2-ethyl-1-[4-(4-fluorobenzyloxy) benzyl]benzimidazole, 1-[4-(3,4-dichlorobenzyloxy) benzyl]-6-ethoxycarbonyl-2-ethylbenzimidazole, 6-carboxy-1-[4-(3,4-dichlorobenzyloxy)benzyl]-2-ethylbenzimidazole, 1-(4-biphenylmethyl)-6-(n-butylcarbamoyl)-2-ethylbenzimidazole, 1-(4-biphenylmethyl)-2-ethyl-6-(thiazol-2-ylcarbamoyl) benzimidazole, 1-(4-biphenylmethyl)-2-ethyl-6-(2-pyridylcarbamoyl)benzimidazole, 1-[sec-(2,4-dichlorophenethyl)]-6-ethoxycarbonyl-2-methylbenzimidazole, 6-carboxy-1-[sec-(2,4-dichlorophenethyl)]-2-methylbenzimidazole, 1-(4-biphenylmethyl)-2-ethyl-6-(phenylcarbamoyl) benzimidazole, 1-(4-biphenylmethyl)-2-ethyl-6-(1,3,4-thiadiazol-2-ylcarbamoyl)benzimidazole, 1-(4-biphenylmethyl)-2-ethyl-6-(tetrazol-5-ylcarbamoyl) benzimidazole, 1-(4-biphenylmethyl)-2-ethyl-6-(1,3,4-triazol-3-ylcarbamoyl)benzimidazole, 1-(4-biphenylmethyl)-2-ethyl-(1,3,4-triazol-2-ylcarbamoyl) benzimidazole, 1-(4-biphenylmethyl)-2-ethyl-6-(3-pyridylcarbamoyl)benzimidazole, 1-(4-biphenylmethyl)-2-ethyl-6-(4-pyridylcarbamoyl)benzimidazole, 1-(2,4-dichlorobenzyl)-2,4-dimethyl-6-methoxycarbonylbenzimidazole, 6-carboxy-1-(2,4-dichlorobenzyl)-2,4-dimethylbenzimidazole, 6-ethoxycarbonyl-2-methyl-1-(4-phenoxybenzyl) benzimidazole, 6-carboxy-2-methyl-1-(4-phenoxybenzyl) benzimidazole, 6-ethoxycarbonyl-2-methyl-1-(2-pyridylmethyl)benzimidazole, 6-carboxy-2-methyl-1-(2-pyridylmethyl)benzimidazole, 6-ethoxycarbonyl-2-methyl-1-(4-nitrobenzyl)benzimidazole, 1-(4-aminobenzyl)-6-ethoxycarbonyl-2-methylbenzimidazole, 1-[(4-benzoylamino)benzyl]-6-ethoxycarbonyl-2-methylbenzimidazole, 1-[(4-benzoylamino)benzyl]-6-carboxy-2-methylbenzimidazole, 6-ethoxycarbonyl-2-methyl-1-[4-(2-phenylethenyl)benzyl]benzimidazole, 6-ethoxycarbonyl-2-methyl-1-[4-(2-phenylethyl)benzyl] benzimidazole, 6-carboxy-2-methyl-1-[4-(2-phenylethyl) benzyl]benzimidazole, 1-[(4-benzoyl)benzyl]-6-ethoxycarbonyl-2-methylbenzimidazole, 1-[(4-benzoyl) benzyl]-6-carboxy-2-methylbenzimidazole, 6-carboxy-2-methyl-[4-(2-phenylethenyl)benzyl]benzimidazole, 1-(dibenzofuran-2-ylmethyl)-6-ethoxycarbonyl-2-methylbenzimidazole, 6-carboxy-1-(dibenzofuran-2-ylmethyl)-2-methylbenzimidazole, 6-ethoxycarbonyl-2-methyl-1-(2-quinolylmethyl)benzimidazole, 6-carboxy-2-methyl-(2-quinolylmethyl)-benzimidazole, 1-(2,4-dichlorobenzyl)-2-hydroxy-6-ethoxycarbonylbenzimidazole, 6 -ethoxycarbonyl-2-methyl-1-[3-(4-bromoisoquinolyl)methyl]benzimidazole, and 6-carboxy-2-methyl-[3-(4-bromoisoquinolyl)methyl] benzimidazole, etc.

Specific examples of benzimidazole derivatives of formula (XI) include 1-(2-chlorobenzyl)-6-ethoxycarbonyl-2-phenylbenzimidazole, 2-benzyl-5-carboxy-1-(2-chlorobenzyl)benzimidazole, 2-benzyl-6-carboxy-1-(2-chlorobenzyl)benzimidazole, 2-benzyl-5-carboxy-1-(2,4-dichlorobenzyl)benzimidazole, 2-benzyl-6-carboxy-1-(2,4-dichlorobenzyl)benzimidazole, 2-benzyl-1-(2-

chlorobenzyl)-6-ethoxycarbonylbenzimidazole, 2-benzyl-1-(2-chlorobenzyl)-5-ethoxycarbonylbenzimidazole, 2-benzyl-1-(2,4-dichlorobenzyl)-6-ethoxycarbonylbenzimidazole, 2-benzyl-1-(2,4-dichlorobenzyl)-5-ethoxycarbonylbenzimidazole, 1-(2-chlorobenzyl)-2-methylbenzimidazole-6-acetic acid, methyl 1-(2-chlorobenzyl)-2-methyl-benzimidazole-6-acrylate, 1-(2-chlorobenzyl)-2-methylbenzimidazole-6-acrylic acid, 1-(2-chlorobenzyl)-6-[2-(pyridylmethyl)carbamoyl] benzimidazole, 1-(biphenyl-4-ylmethyl)-6-ethoxycarbonyl-2-methoxymethylbenzimidazole, 1-(biphenyl-4-ylmethyl)-6-carboxy-2-methoxymethyl-benzimidazole, 1-(4-benzyloxybenzyl)-6-ethoxycarbonyl-2-methoxymethylbenzimidazole, 1-(4-benzyloxybenzyl)-6-carboxy-2-methoxymethylbenzimidazole, 1-(2,4-dichlorobenzyl)-6-ethoxycarbonyl-2-methoxymethyl-benzimidazole, and 6-carboxy-1-(2,4-dichlorobenzyl)-2-methoxymethyl benzimidazole, etc.

Specific examples of benzimidazole derivatives of formula (XII) include 6-t-butoxycarbonylamino-1-(2-chlorobenzyl)-2-n-propylbenzimidazole, 1-(2-chlorobenzyl)-6-mesylamino-2-n-propylbenzimidazole, 6-acetylamino-1-(2-chlorobenzyl)-2-n-propylbenzimidazole, 6-amino-1-(2-chlorobenzyl)-2-n-propylbenzimidazole, 1-(2-chlorobenzyl)-2-n-propyl-6-ureidobenzimidazole, 6-t-butoxycarbonylamino-1-(2-chlorobenzyl)-2-methylbenzimidazole, 6-amino-1-(2-chlorobenzyl)-2-methylbenzimidazole, and 6-(1-butanesulfonylamino)-1-(2-chlorobenzyl)-2-methylbenzimidazole, etc.

Specific examples of benzimidazole derivatives of formula (XIII) include 1-(2-chlorobenzyl)-6-cyano-2-cyclopropylbenzimidazole, and 1-(2-chlorobenzyl)-6-cyano-2-n-propylbenzimidazole, etc. Specific examples of benzimidazole derivatives of formula (VI) include 1-(2-chlorobenzyl)-6-(4-dimethylaminophenylmethylcarbamoyl)-2-n-propylbenzimidazole, 1-(2-chlorobenzyl)-2-n-propyl-6-thiomorpholinocarbonylbenzimidazole, 1-(2-chlorobenzyl)-2-cyclopropyl-6-(2-pyridylcarbamoyl)benzimidazole, 6-(2-carboxy-1-pyrrolidinocarbonyl)-1-(2-chlorobenzyl)-2-n-propylbenzimidazole, 1-(2-chlorobenzyl)-6-[N-methyl-N-(2-pyridylmethyl)carbamoyl]-2-n-propylbenzimidazole, 1-(2-chlorobenzyl)-6-piperonylcarbamoyl-2-n-propylbenzimidazole, 1-(2-chlorobenzyl)-6-(homopiperidinocarbonyl)-2-n-propylbenzimidazole, 1-(2-chlorobenzyl)-6-[N-methyl-N-(2-pyridyl)carbamoyl]-2-n-propylbenzimidazole, 2-n-butyl-1-(2-(fluorobenzyl)-6-[N-methyl-N-(2-pyridylmethyl)carbamoyl]benzimidazole, 2-cyclopropyl-1-(2-fluorobenzyl)-6-(piperonylcarbamoyl) benzimidazole, 2-[[1-(2-chlorobenzyl)-2-ethylbenzimidazol-6-yl]carbonylaminomethyl]pyridine-1-oxide, and 1-(2,4-dichlorobenzyl)-2-methyl-6-(2-pyridylcarbamoyl)benzimidazole, etc.

The present invention further includes, within its scope, the following novel benzimidazole derivatives: 1-(2-bromobenzyl)-6-ethoxycarbonyl-2-n-propylbenzimidazole, 6-ethoxycarbonyl-1-(2-fluorobenzyl)-2-n-propylbenzimidazole, 6-ethoxycarbonyl-1-(4-fluorobenzyl)-2-n-propylbenzimidazole, 6-ethoxycarbonyl-1-(3-fluorobenzyl)-2-n-propylbenzimidazole, 1-(2,6-dichlorobenzyl)-6-ethoxycarbonyl-2-n-propylbenzimidazole, 1-(3-methylbenzyl)-6-ethoxycarbonyl-2-n-propylbenzimidazole, 2-cyclopropyl-6-ethoxycarbonyl-1-(2-fluorobenzyl)-benzimidazole, 1-(2-chlorobenzyl)-2-cyclobutyl-6-ethoxycarbonylbenzimidazole, 1-(2-chlorobenzyl)-6-ethoxycarbonyl-2-n-pentylbenzimidazole, 5-carboxy-1-(2-chlorobenzyl)-2-n-propylbenzimidazole, 6-carboxy-1-(3-methylbenzyl)-2-n-propylbenzimidazole, 2-n-butyl-7-carboxy-1-(2-chlorobenzyl)benzimidazole, 6-carboxy-1-(2-fluorobenzyl)-2 -cyclopropylbenzimidazole, 2-n-butyl-6-carboxy-1-(2-fluorobenzyl)benzimidazole, 1-(2-chlorobenzyl)-6-chlorocarbonyl-2-cyclopropylbenzimidazole, 1-(2-chlorobenzyl)-6-morpholinocarbamoyl-2-n-propylbenzimidazole, 2-n-butyl-1-(2-chlorobenzyl)-6-[(2-pyridylmethyl)carbamoyl] benzimidazole, 2-n-butyl-5-carbamoyl-1-(2-chlorobenzyl) benzimidazole, 1-(2-chlorobenzyl)-2-cyclopropyl-6-morpholinocarbonylbenzimidazole, 1-(2-chlorobenzyl)-2-cyclopropyl-6-[(2-pyridylmethyl)carbamoyl] benzimidazole, 1-(2-chlorobenzyl)-2-cyclobutyl-6-[(2-pyridylmethyl)carbamoyl]benzimidazole, 1-(2-chlorobenzyl)-2-n-propyl-5-[(2-pyridylmethyl)carbamoyl] benzimidazole, 1-(2-chlorobenzyl)-6-phenylcarbamoyl-2-n-propylbenzimidazole, 1-(2-chlorobenzyl)-2-n-propyl-6-[(4-pyridylmethyl)carbamoyl]benzimidazole, 1-(2-chlorobenzyl)-2-n-propyl-6-[(3-pyridylmethyl)carbamoyl] benzimidazole, 1-(3-methylbenzyl)-2-n-propyl-6-[(2-pyridylmethyl)carbamoyl]benzimidazole, 1-(2-chlorobenzyl)-2-ethyl-6-[(2-pyridylmethyl)carbamoyl] benzimidazole, 2-n-butyl-1-(2-chlorobenzyl)-7-[(2-pyridylmethyl)carbamoyl]benzimidazole, 2-n-butyl-1-(2-fluorobenzyl)-6-(2-pyridylmethylcarbamoyl) benzimidazole, 1-(2-chlorobenzyl)-6-ethoxycarbonyl-2-methylbenzimidazole, 1-(3-chlorobenzyl)-6-ethoxycarbonyl-2-n-propylbenzimidazole, 1-benzyl-6-ethoxycarbonyl-2-n-propylbenzimidazole, 1-(4-chlorobenzyl)-6-ethoxycarbonyl-2-n-propylbenzimidazole, 6-ethoxycarbonyl-2-methyl-1-[2-(trifluoromethyl)benzyl] benzimidazole, 6-ethoxycarbonyl-2-methyl-1-[4-(trifluoromethyl)benzyl]benzimidazole, 1-(3,4-dichlorobenzyl)-6-ethoxycarbonyl-2-methylbenzimidazole, 6-ethoxycarbonyl-2-methyl-1-(2-methylbenzyl) benzimidazole, 1-benzyl-6-ethoxycarbonyl-2-methylbenzimidazole, 1-(4-t-butylbenzyl)-6-ethoxycarbonyl-2-methylbenzimidazole, 1-(2-chlorobenzyl)-5-ethoxycarbonyl-2-methylbenzimidazole, 1-(2,6-dichlorobenzyl)-6-ethoxycarbonyl-2-methylbenzimidazole, 1-(2,4-dichlorobenzyl)-6-ethoxycarbonyl-2-methylbenzimidazole, 6-carboxy-1-(4-chlorobenzyl)-2-n-propylbenzimidazole, 6-carboxy-1-(2,6-dichlorobenzyl)-2-methylbenzimidazole, 6-carboxy-2-methyl-1-[2-(trifluoromethyl)benzyl]benzimidazole, 6-carboxy-2-methyl-1-[4-(trifluoromethyl)benzyl] benzimidazole, 6-carboxy-1-(3,4-dichlorobenzyl)-2-methylbenzimidazole, 1-benzyl-6-carboxy-2-n-propylbenzimidazole, 6-carboxy-1-(3-chlorobenzyl)-2-n-propylbenzimidazole, 6-carboxy-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole, 1-(4-t-butylbenzyl)-6-carboxy-2-methylbenzimidazole, 6-carboxy-2-methyl-1-(2-methylbenzyl)benzimidazole, 1-benzyl-6-carboxy-2-methylbenzimidazole, 5-carboxy-1-(2-chlorobenzyl)-2-methylbenzimidazole, 6-carboxy-1-(2-chlorobenzyl)-2-methylbenzimidazole, 1-(2,4-dichlorobenzyl)-2-methyl-6-[(2-pyridylmethyl)carbamoyl]benzimidazole, 1-(2-chlorobenzyl)-2-methyl-6-[(2-pyridylmethyl)carbamoyl] benzimidazole, 1-(3-chlorobenzyl)-2-n-propyl-6-[(2-pyridylmethyl)carbamoyl]benzimidazole, 1-benzyl-2-n-propyl-6-[(2-pyridylmethyl)carbamoyl]benzimidazole, 1-(4-chlorobenzyl)-2-propyl-6-[(2-pyridylmethyl) carbamoyl]benzimidazole, 1-(2,6-dichlorobenzyl)-2-methyl-6-[(2-pyridylmethyl)carbamoyl]benzimidazole, 2-methyl-6-[(2-pyridylmethyl)carbamoyl]-1-[2-

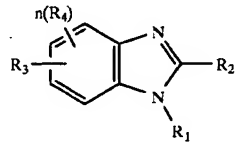
(trifluoromethyl)benzyl]benzimidazole, 2-methyl-6-[(2-pyridylmethyl)carbamoyl]-1-[4-(trifluoromethyl)benzyl] benzimidazole, 1-(3,4-dichlorobenzyl)-2-methyl-6-[(2-pyridylmethyl)carbamoyl]benzimidazole, 2-methyl-1-(2-methylbenzyl)-6-[(2-pyridylmethyl)carbamoyl] benzimidazole, 1-benzyl-2-methyl-6-[(2-pyridylmethyl) carbamoyl]benzimidazole, 1-(4-t-butylbenzyl)-2-methyl-6-[(2-pyridylmethyl)carbamoyl]benzimidazole, 6-carbamoyl-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole, 1-(2,4-difluorobenzyl)-2-methyl-6-[(2-pyridylmethyl)carbamoyl] benzimidazole, 1-(2,4-difluorobenzyl)-2-methyl-5-[(2-pyridylmethyl)carbamoyl]benzimidazole, 1-(2,4-dichlorobenzyl)-7-ethoxycarbonyl-2-methylbenzimidazole, 7-carboxy-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole, 1-(2,4-dichlorobenzyl)-4-ethoxycarbonyl-2-methylbenzimidazole, 4-carboxy-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole, 1-(2,4-dichlorobenzyl)-5-ethoxycarbonyl-2-methylbenzimidazole, 5-carboxy-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole, and 6-(n-butylcarbamoyl)-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole.

The benzimidazole derivatives and their pharmaceutically acceptable salts of the present invention that are mentioned hereinabove are effective for preventing and treating various disorders of, for example, impaired glucose tolerance, diabetes (type II diabetes), diabetic complications (e.g., diabetic nephropathy, diabetic neuropathy, diabetic retinopathy, etc.), syndrome of insulin resistance (e.g., insulin receptor disorders, Rabson-Mendenhall syndrome, leprechaunism, Kobberling-Dunnigan syndrome, Seip syndrome, Lawrence syndrome, Cushing syndrome, acromegaly, etc.), hyperlipidemia, atherosclerosis, cardiovascular disorders (e.g., stenocardia; cardiac failure, etc.), hyperglycemia (e.g., abnormal saccharometabolism such as feeding disorders, etc.), and hypertension based on their blood sugar level-depressing activity, as well as stenocardia, hypertension, pulmonary hypertension, congestive heart failure, glomerulopathy (e.g., diabetic glomerulosclerosis, etc.), tubulointerstitial disorders (e.g., renopathy induced by FK506, cyclosporin, etc.), renal failure, atherosclerosis, angiostenosis (e.g., after percutaneous arterioplasty), distal angiopathy, cerebral apoplexy, chronic reversible obstructions (e.g., bronchitis, asthma (chronic asthma, allergic asthma), etc.), allergic rhinitis, urticaria, glaucoma, diseases characterized by enteromotility disorders (e.g., hypersensitive enteropathy syndrome, etc.), impotence (e.g., organic impotence, psychic impotence, etc.), and diabetic complications (e.g., diabetic gangrene, diabetic arthropathy, diabetic glomerulosclerosis, diabetic dermatopathy, diabetic neuropathy, diabetic cataract, diabetic retinopathy, etc.), nephritis, cancerous cachexia, and restenosis after PTCA based on their cGMP-PDE (especially PDE-V)-inhibiting activity, smooth muscle relaxing activity, bronchodilating activity, vasodilating activity, smooth muscle cell suppressing activity, and antiallergic activity.

In addition, we, the present inventors, have further found that the benzimidazole derivatives which we have disclosed in Japanese Patent Application Laid-Open No. 5-222000 as c-GMP phosphodiesterase inhibitors also have the above-mentioned activities, and have now confirmed that these benzimidazole derivatives are also effective for preventing and treating the above-mentioned diseases and disorders like the compounds mentioned hereinabove.

Accordingly, the present invention further includes pharmaceutical compositions comprising, as an active ingredient, any of benzimidazole derivatives of the following formula (I) and their pharmaceutically acceptable salts, which are effective for preventing and treating impaired glucose tolerance, diabetes (type II diabetes), diabetic complications (e.g., diabetic nephropathy, diabetic neuropathy, diabetic retinopathy, etc.), syndrome of insulin resistance (e.g., insulin receptor disorders, Rabson-Mendenhall syndrome, leprechaunism, Kobberling-Dunnigan syndrome, Seip syndrome, Lawrence syndrome, Cushing syndrome, acromegaly, etc.), hyperlipidemia, atherosclerosis, cardiovascular disorders (e.g., stenocardia, cardiac failure, etc.), hyperglycemia (e.g., abnormal saccharometabolism such as feeding disorders, etc.), or hypertension; or stenocardia, hypertension, pulmonary hypertension, congestive heart failure, glomerulopathy (e.g., diabetic glomerulosclerosis, etc.), tubulointerstitial disorders (e.g., renopathy induced by FK506, cyclosporin, etc.), renal failure, atherosclerosis, angiostenosis (e.g., after percutaneous arterioplasty), distal angiopathy, cerebral apoplexy, chronic reversible obstructions (e.g., bronchitis, asthma (chronic asthma, allergic asthma), etc.), allergic rhinitis, urticaria, glaucoma, diseases characterized by enteromotility disorders (e.g., hypersensitive enteropathy syndrome, etc.), impotence (e.g., organic impotence, psychic impotence, etc.), and diabetic complications (e.g., diabetic gangrene, diabetic arthropathy, diabetic glomerulosclerosis, diabetic dermatopathy, diabetic neuropathy, diabetic cataract, diabetic retinopathy, etc.), nephritis, cancerous cachexia, or restenosis after PTCA.

(I)



In formula (I):

R_1 represents a hydrogen atom, an arylsulfonyl group, or a lower alkyl group; and said lower alkyl group may be substituted by an aryl group or an aryl group substituted by one or two substituents selected from a halogen atom, a haloaryl group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, a nitro group, an amino group, a cyano group, an aryl group, an aryl-lower alkyl group, an aryl-lower alkyloxy group, a haloaryl-lower alkyloxy group, an arylsulfonyl-lower alkyl group, an arylsulfonylamino group, a cyanoaryl group, and a heterocyclic group, or by a heterocyclic group;

R_2 represents a hydrogen atom, a lower cycloalkyl group, a hydroxyl group, a lower alkoxy group, a mercapto group, a lower alkylthio group, an amino group, a lower alkylamino group, a carboxyl group, an aryl group, or a lower alkyl group; and said lower alkyl group may be substituted by a halogen atom, a lower alkoxy group, a cyano group, a chlorocarbonyl group, an aryl group, or a heterocyclic group;

R_3 represents a carboxyl group, an esterified carboxyl group, an amidated carboxyl group, an amino group, an amido group, or a sulfonyl group; and said amino group and said amido group may be substituted by an acyl group or a sulfonyl group; and a halogen atom, an amino group, or an acylamino group is bonded to said sulfonyl group; or R_3 may be bonded to the skeleton via a lower alkylene or alkenylene group; and

R_4 represents a neutral substituent. R_4 includes a halogen atom, and a lower alkyl group, an aralkyl group, an

alkynyl group, a lower alkyloxy group, and halogen-substituted groups of these. Where R_4 is a hydrocarbon group, it may be either saturated or unsaturated, or either linear or cyclic, or may even be branched. For the halogen atom and the halogen-substituted groups, the kind of the halogen is not specifically defined. For the latter, the number of halogens substituted is not specifically defined.

n means an integer from 0 to 3. Thus, one, two or three R_4s may be bonded to the skeleton, or no R_4 may be bonded thereto. The position of R_4 may be any of the ortho-position, the meta-position and the para-position relative to the other substituent.

Specific examples of benzimidazole derivatives of formula (I) include 2-butyl-1-(2-chlorobenzyl)-6-ethoxycarbonylbenzimidazole, 1-(4-bromo-2-fluorobenzyl)-2-butyl-6-ethoxycarbonylbenzimidazole, 2-butyl-1-(2,4-dichlorobenzyl)-6-ethoxycarbonylbenzimidazole, 2-butyl-6-ethoxycarbonyl-1-(4-methoxycarbonylbenzyl)benzimidazole, 2-butyl-6-ethoxycarbonyl-1-(2-fluorobenzyl)benzimidazole, 2-butyl-6-ethoxycarbonyl-1-(2-trifluoromethylbenzyl) benzimidazole, 1-(2-chlorobenzyl)-6-ethoxycarbonyl-2-ethylbenzimidazole, 1-(2-chlorobenzyl)-6-ethoxycarbonyl-2-propylbenzimidazole, 1-(2-chlorobenzyl)-2-cyclopropyl-6-ethoxycarbonylbenzimidazole, 1-(2-chlorobenzyl)-6-ethoxycarbonyl-2-isopropylbenzimidazole, 2-butyl-1-(2-chlorobenzyl)-5-ethoxycarbonylbenzimidazole, 2-butyl-1-(2-chlorobenzyl)-7-ethoxycarbonylbenzimidazole, 1-(2-chlorobenzyl)-5-ethoxycarbonyl-2-propylbenzimidazole, 2-butyl-1-(2-chlorobenzyl)-6-carboxybenzimidazole, 2-butyl-6-carboxy-1-(4-carboxybenzyl)benzimidazole, 6-carboxy-1-(2-chlorobenzyl)-2-ethylbenzimidazole, 6-carboxy-1-(2-chlorobenzyl)-2-propylbenzimidazole, 6-carboxy-1-(2-chlorobenzyl)-2-cyclopropylbenzimidazole, 2-butyl-5-carboxy-1-(2-chlorobenzyl)imidazole, 2-butyl-1-(2-chlorobenzyl)-6-dimethylcarbamoylbenzimidazole, 6-(benzylcarbamoyl)-2-butyl-1-(2-chlorobenzyl) benzimidazole, 2 -butyl-1-(2-chlorobenzyl)-6-morpholinocarbonylbenzimidazole, 2-butyl-6-carbamoyl-(2-chlorobenzyl)-benzimidazole, 2-butyl-1-(2-chlorobenzyl)-6-(4-methylpiperazinyl) carbonylbenzimidazole, 2-butyl-1-(2-chlorobenzyl)-6-(methylcarbamoyl)benzimidazole, 6-carbamoyl-1-(2-chlorobenzyl)-2-ethylbenzimidazole, 6-carbamoyl-1-(2-chlorobenzyl)-2-propylbenzimidazole, 6-carbamoyl-1-(2-chlorobenzyl)-2-cyclopropylbenzimidazole, 2-butyl-5-carbamoyl-1-(2-chlorobenzyl)benzimidazole, 2-butyl-1-(2-chlorobenzyl)-6-(isopropylcarbonyl)benzimidazole, 1-(2-chlorobenzyl)-6-chloroformyl-2-propylbenzimidazole, 1-(2-chlorobenzyl)-6-(methylcarbamoyl)-2-propylbenzimidazole, 1-(2-chlorobenzyl)-6-(ethylcarbamoyl)-2-propylbenzimidazole, 1-(2-chlorobenzyl)-6-(isopropyl)carbamoyl-2-propylbenzimidazole, 1-(2-chlorobenzyl)-6-(piperidinocarbonyl)-2-propylbenzimidazole, 1-(2-chlorobenzyl)-6-(morpholinocarbonyl)-2-propylbenzimidazole, 1-(2-chlorobenzyl)-6-(2-morpholinoethyl)carbamoyl-2-propylbenzimidazole, 1-(2-chlorobenzyl)-6-[4-(2-hydroxyethyl)piperazinyl]carbonyl-2-propylbenzimidazole, 1-(2-chlorobenzyl)-2-propyl-6-(2-pyridylmethyl)carbamoylbenzimidazole, 1-(2-chlorobenzyl)-2-propyl-6-[4-(4-phenyl-1,2,3,6-tetrahydropyridin-1-yl)butyl]carbamoylbenzimidazole, etc.

To use the benzimidazole derivatives of the present invention for treating diseases or disorders such as those mentioned hereinabove, they may be formulated into pharmaceutical compositions of ordinary forms, which comprise, as an active ingredient, any of the derivatives along with pharmaceutically acceptable carriers, such as organic or inorganic solid or liquid vehicles, and which are suitable for peroral administration, parenteral administration or external application. The pharmaceutical compositions may be of any solid form of tablets, granules, powders, capsules, etc., or may be of any liquid form of solutions, suspensions, syrups, emulsions, lemonades, etc.

If desired, the pharmaceutical compositions may further contain a pharmaceutical aid, a stabilizer, a wetting agent, and also any ordinary additive of, for example, lactose, citric acid, tartaric acid, stearic acid, magnesium stearate, terra alba, sucrose, corn starch, talc, gelatin, agar, pectin, peanut oil, olive oil, cacao butter, ethylene glycol, etc.

The amount of the above-mentioned derivative of the present invention to be used shall vary, depending on the age and the condition of patients, the type and the condition of diseases or disorders, and the type of the derivative to be used. In general, for peroral administration, the dose of the derivative may be from 1 to 100 mg/kg; and for intramuscular injection or intravenous injection, it may be from 0.1 to 10 mg/kg. Such a unit dose may be applied to a patient once to four times a day.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** shows chemical formulae of compound (42) to compound (47).

FIG. **2** shows chemical formulae of compound (48) to compound (53).

FIG. **3** shows chemical formulae of compound (54) to compound (59).

FIG. **4** shows chemical formulae of compound (60) to compound (65).

FIG. **5** shows chemical formulae of compound (66) to compound (71).

FIG. **6** shows chemical formulae of compound (72) to compound (77).

FIG. **7** shows chemical formulae of compound (78) to compound (83).

FIG. **8** shows chemical formulae of compound (84) to compound (89).

FIG. **9** shows chemical formulae of compound (90) to compound (95).

FIG. **10** shows chemical formulae of compound (96) to compound (101).

FIG. **11** shows chemical formulae of compound (102) to compound (107).

FIG. **12** shows chemical formulae of compound (108) to compound (113).

FIG. **13** shows chemical formulae of compound (114) to compound (119).

FIG. **14** shows chemical formulae of compound (120) to compound (125).

FIG. **15** shows chemical formulae of compound (126) to compound (131).

FIG. **16** shows chemical formulae of compound (132) to compound (137).

FIG. **17** shows chemical formulae of compound (138) to compound (143).

FIG. **18** shows chemical formulae of compound (144) to compound (149).

FIG. **19** shows chemical formulae of compound (150) to compound (155).

FIG. **20** shows chemical formulae of compound (156) to compound (161).

FIG. **21** shows chemical formulae of compound (162) to compound (167).

FIG. **22** shows chemical formulae of compound (168) to compound (173).

FIG. **23** shows chemical formulae of compound (174) to compound (179).

FIG. **24** shows chemical formulae of compound (180) to compound (185).

FIG. **25** shows chemical formulae of compound (186) to compound (191).

FIG. **26** shows chemical formulae of compound (192) to compound (197).

FIG. **27** shows chemical formulae of compound (198) to compound (203).

FIG. **28** shows chemical formulae of compound (204) to compound (209).

FIG. **29** shows chemical formulae of compound (210) to compound (215).

FIG. **30** shows chemical formulae of compound (216) to compound (221).

FIG. **31** shows chemical formulae of compound (222) to compound (227).

FIG. **32** shows chemical formulae of compound (228) to compound (233).

FIG. **33** shows chemical formulae of compound (234) to compound (239).

FIG. **34** shows chemical formulae of compound (240) to compound (245).

FIG. **35** shows chemical formulae of compound (246) to compound (251).

FIG. **36** shows chemical formulae of compound (252) to compound (257).

FIG. **37** shows chemical formulae of compound (258) to compound (263).

FIG. **38** shows chemical formulae of compound (264) to compound (269).

FIG. **39** shows chemical formulae of compound (270) to compound (275).

FIG. **40** shows chemical formulae of compound (276) to compound (281).

FIG. **41** shows chemical formulae of compound (282) to compound (287).

FIG. **42** shows chemical formulae of compound (288) to compound (293).

FIG. **43** shows chemical formulae of compound (294) to compound (299).

FIG. **44** shows chemical formulae of compound (300) to compound (305).

FIG. **45** shows chemical formulae of compound (306) to compound (311).

FIG. **46** shows chemical formulae of compound (312) to compound (316).

FIG. **47** shows chemical formulae of compound (317) to compound (322).

FIG. **48** shows chemical formulae of compound (323) to compound (328).

FIG. **49** shows chemical formulae of compound (329) to compound (334).

FIG. **50** shows chemical formulae of compound (335) to compound (340).

FIG. **51** shows chemical formulae of compound (341) to compound (346).

FIG. **52** shows chemical formulae of compound (347) to compound (352).

FIG. **53** shows chemical formulae of compound (353) to compound (358).

FIG. **54** shows chemical formulae of compound (359) to compound (364).

FIG. **55** shows chemical formulae of compound (365) to compound (370).

FIG. **56** shows chemical formulae of compound (371) to compound (376).

FIG. **57** shows chemical formulae of compound (377) to compound (382).

FIG. **58** shows chemical formulae of compound (383) to compound (386).

BEST MODE FOR CARRYING OUT THE INVENTION

The present invention is illustrated more specifically by referring to the following Examples. However, the present invention is not limited thereto.

PRODUCTION EXAMPLE 1

Production of ethyl 3-[N-(2-bromobenzyl) butyrylamino]-4 -nitrobenzoate

One-hundred milligrams of sodium hydride (60% water-in-oil suspension) were added to a solution of 247 mg of ethyl 3-butyrylamino-4-nitrobenzoate in 10 ml of N,N-dimethylformamide in a nitrogen atmosphere at room temperature in some divided portions. The reaction suspension was stirred at the same temperature for 1 hour, and a solution of 244 mg of 2-bromobenzyl bromide in 2 ml of N,N-dimethylformamide was gradually added dropwise thereto over a period of 10 minutes. The reaction mixture was stirred at room temperature for 1 hour, and was poured in ice water. The oily substance precipitated was extracted with methylene chloride. The organic solvent layer was washed with water, dried, and then concentrated under reduced pressure. The residue was developed through silica-gel flash column chromatography, and was eluted with a mixture of 25% ethyl acetate and n-hexane to give 540 mg of yellow oil of ethyl 3-[N-(2-bromobenzyl)butyrylamino-4-nitrobenzoate.

Properties of the compound:

^{1}H-NMR ($CDCl_3$, δ): 0.87 (3H, t, J=8 Hz), 1.48 (3H, t, J=8 Hz), 1.68 (2H, sextet, J=8 Hz), 2.03 (2H, t, J=8 Hz), 4.30–4.46 (2H, m), 4.70 (1H, d, J=15 Hz), 5.40 (1H, d, J=15 Hz), 7.08–7.34 (2H, m), 7.43 (1H, dd, J=1, 8 Hz), 7.58 (1H, dd, J=1, 8 Hz), 7.66 (1H, d, J=1 Hz), 7.96 (1H, d, J=8 Hz 8.16 (1H, dd, J=1, 8 Hz).

PRODUCTION EXAMPLE 2

Production of ethyl 3-[N-(2-chlorobenzyl) benzoylamino]-4-nitrobenzoate

In the same manner as in Production Example 1, 480 mg of yellow crystals of ethyl 3-[N-(2-chlorobenzyl) benzoylamino]-4-nitrobenzoate were formed from 450 mg of ethyl 3-benzoylamino-4-nitrobenzoate and 243 mg of 2-chlorobenzyl bromide.

Properties of the compound:

^{1}H-NMR ($CDCl_3$, δ): 1.35 (3H, t, J=8 Hz), 4.35 (2H, q, J=8 Hz), 4.76 (1H, bd, J=15 Hz), 5.82 (1H, bd, J=15 Hz), 7.10–8.00 (12H, m).

mp: 111–113° C.

PRODUCTION EXAMPLE 3

Production of ethyl 3-[N-(2-fluorobenzyl) butyrylamino]-4-nitrobenzoate

In the same manner as in Production Example 1, 394 mg of yellow oil of ethyl 3-[N-(2-fluorobenzyl)butyrylamino]-4-nitrobenzoate were formed from 300 mg of ethyl 3-butyrylamino-4-nitrobenzoate and 243 mg of 2-fluorobenzyl bromide.

Properties of the compound:

^{1}H-NMR ($CDCl_3$, δ): 0.85 (3H, t, J=8 Hz), 1.40 (3H, t, J=8 Hz), 1.65 (2H, sextet, J=8 Hz), 1.98 (2H, t, J=8 Hz), 4.30–4.45 (2H, m), 4.60 (1H, d, J=10 Hz), 5.25 (1H, d, J=10 Hz), 6.88 (2H, t, J=8 Hz), 7.08 (2H, dd, J=5, 8 Hz), 7.24 (1H, dt, J=1, 8 Hz), 7.41 (1H, dt, J=1, 8 Hz), 7.69 (1H, d, J=1 Hz), 7.96 (1H, d, J=8 Hz), 8.15 (1H, dd, J=1, 8 Hz).

PRODUCTION EXAMPLE 4

Production of ethyl 3-[N-(4-fluorobenzyl) butyrylamino]-4-nitrobenzoate

In the same manner as in Production Example 1, 400 mg of yellow oil of ethyl 3-[N-(4-fluorobenzyl)butyrylamino]-4-nitrobenzoate were formed from 300 mg of ethyl 3-butyrylamino-4-nitrobenzoate and 243 mg of 4-fluorobenzyl bromide.

Properties of the compound:

^{1}H-NMR ($CDCl_3$, δ): 0.86 (3H, t, J=8 Hz), 1.37 (3H, t, J=8 Hz), 1.56–1.76 (2H, m), 1.96–2.04 (2H, m), 4.32–4.46 (2H, m), 4.40 (1H, d, J=14 Hz), 5.23(1H, d, J=14 Hz), 6.95 (2H, t, J=8 Hz), 7.10 (2H, dd, J=5, 8 Hz), 7.47 (1H, d, J=1 Hz), 7.95 (1H, d, J=8 Hz), 8.16 (1H, dd, J=1, 8 Hz).

PRODUCTION EXAMPLE 5

Production of ethyl 3-[N-(2-cyanobenzyl) butyrylamino]-4-nitrobenzoate

Potassium carbonate (296 mg) was added to a solution of 200 mg of ethyl 3-butyrylamino-4-nitrobenzoate and 154 mg of 2-cyanobenzyl bromide in N,N-dimethylformamide, and the mixture was stirred at 20° C. for 3 hours. The reaction mixture was extracted with ethyl acetate and with water. The organic layer was washed with water and with a sodium chloride aqueous solution, and was then dried over magnesium sulfate. The solvent was distilled off under reduced pressure to give 330 mg of yellow oil of ethyl 3-[N-(2-cyanobenzyl)butyrylamino]-4-nitrobenzoate.

Properties of the compound:

^{1}H-NMR ($CDCl_3$, δ): 0.86 (3H, t, J=8 Hz), 1.49 (3H, t, J=8 Hz), 1.67 (2H, sextet, J=8 Hz), 2.02 (2H, t, J=8 Hz), 4.28–4.52 (2H, m), 4.90 (1H, d, J=15 Hz), 5.28 (1H, d, J=15 Hz), 7.40 (1H, t, J=8 Hz), 7.61 (1H, dt, J=1, 8 Hz), 7.70 (1H, d, J=1 Hz), 7.74 (1H, dd, J=1, 8 Hz), 8.02 (1H, d, J=10 Hz), 8.22 (1H, dd, J=1, 10 Hz).

PRODUCTION EXAMPLE 6

The following compounds were produced in the same manner as in Production Example 5.

PRODUCTION EXAMPLE 6-1

Ethyl 3-[N-(3-fluorobenzyl)butyrylamino]-4-nitrobenzoate

Properties of the compound:

yellow oil.

^{1}H-NMR ($CDCl_3$, δ): 0.86 (3H, t, J=7.5 Hz), 1.35 (3H, t, J=7.5 Hz), 1.68 (2H, m), 2.00 (2H, t, J=7.5 Hz), 4.36 (1H, d, J=15 Hz), 4.40 (2H, m), 5.31 (1H, d, J=15 Hz), 6.85–7.28 (4H, m), 7.60 (1H, d, J=1.5 Hz), 7.97 (1H, d, J=10 Hz), 8.16 (1H, dd, J=10,1.5 Hz).

PRODUCTION EXAMPLE 6-2

Ethyl 4-nitro-3-[N-(2-pyridylmethyl)-n-butyrylamino]benzoate

This compound was used in the subsequent step at once.

Property of the compound:

yellow oil.

PRODUCTION EXAMPLE 6-3

Ethyl 3-[N-(2,6-dichlorobenzyl)butyrylamino]-4-nitrobenzoate

Properties of the compound:

^{1}H-NMR ($CDCl_3$, δ): 0.89 (3H, t, J=7.5 Hz), 1.38 (3H, t, J=7.5 Hz), 1.70 (2H, m), 2.03 (2H, t, J=7.5 Hz), 4.36 (2H, m), 4.96 (1H, d, J=13.5 Hz), 5.70(1H, d, J=13.5 Hz), 7.10–7.28 (3H, m), 7.49 (1H, d, J=1.5 Hz), 8.03 (1H, d, J=7.5 Hz), 8.14 (1H, dd, J=7.5 and 1.5 Hz).

mp: 85–89° C.

PRODUCTION EXAMPLE 6-4

Ethyl 3-[N-(3-methylbenzyl)propionylamino]-4-nitrobenzoate

This compound was used in the subsequent step at once.

Property of the compound:

yellow oil.

PRODUCTION EXAMPLE 6-5

Ethyl 3-[N-(2-fluorobenzyl) cyclopropanecarbonylamino]-4-nitrobenzoate

Properties of the compound:

yellow oil.

^{1}H-NMR ($CDCl_3$, δ): 0.60–0.71 (2H, m), 0.99–1.14 (3H, m), 1.38 (3H, t, J=7.5 Hz), 4.37 (2H, m), 4.62 (1H, d, J=12 Hz), 5.30 (1H, d, J=12 Hz), 6.92 (1H, t, J=7.5 Hz), 7.10 (1H, t, J=7.5 Hz), 7.26 (1H, m), 7.42 (1H, t, J=7.5 Hz), 7.80 (1H, s), 7.99 (1H, d, J=7.5 Hz), 8.14 (1H, dd, J=7.5 and 2 Hz).

PRODUCTION EXAMPLE 6-6

Ethyl 3-[N-(2-chlorobenzyl) cyclobutanecarbonylamino]-4-nitrobenzoate

Properties of the compound:

^{1}H-NMR ($CDCl_3$, δ): 1.37 (3H, t, J=7.5 Hz), 1.68–1.87 (4H, m), 2.22–2.58 (2H, m), 2.75–2.94 (1H, m), 4.23–4.46 (2H, m), 4.63 (1H, d, J=15 Hz), 5.45 (1H, d, J=15 Hz), 7.14–7.24 (3H, m), 7.35–7.45 (1H, m), 7.56 (1H, d, J=2 Hz), 7.97 (1H, d, J=9 Hz), 8.13 (1H, dd, J=9, 2 Hz).

PRODUCTION EXAMPLE 6-7

Ethyl 3-cyclobutanecarbonylamino-4-nitrobenzoate

Properties of the compound:

^{1}H-NMR ($CDCl_3$, δ): 1.43 (3H, t, J=7.5 Hz), 1.86–2.19 (2H, m), 2.22–2.54 (4H, m), 3.20–3.41 (1H, m), 4.43 (2H,

q, J=7.5 Hz), 7.80 (1H, dd, J=10, 2 Hz), 8.26 (1H, d, J=10 Hz), 9.45 (1H, d, J=2 Hz).

mp: 94–96° C.

PRODUCTION EXAMPLE 7

Production of 3-acetylamino-4-nitrobenzamide

Oxalyl chloride (3.91 ml) was added dropwise to a solution of 7.00 g of 3-acetylamino-4-nitrobenzoic acid in 50 ml of dichloromethane in a nitrogen atmosphere while being cooled with ice, and the mixture was stirred for 1 hour while being cooled with ice and then at room temperature for 2.5 hours. The reaction solvent was distilled off under reduced pressure, and the residue was then dissolved in 50 ml of tetrahydrofuran. The solution was added dropwise to 28% aqueous ammonia in a nitrogen atmosphere while being cooled with ice. The reaction solution was stirred for 1 hour, and water and ethyl acetate were added thereto. Approximately 8 g of the solid material precipitated were collected through filtration. After the filtrate was separated, the organic layer was washed with water, and dried over magnesium sulfate. Then, the solvent was distilled off under reduced pressure to obtain the residue. The solid material precipitated and the residue were combined, washed with hot ethyl acetate, and collected through filtration to give 4.94 g of 3-acetylamino-4-nitrobenzamide.

Properties of the compound:

^{1}H-NMR (DMSO-d6, δ): 2.08 (3H, s), 7.68 (1H, br s), 7.78 (1H, dd, J=9, 2 Hz), 7.94–8.05 (2H, m), 8.23 (1H, brs).

Mass (FAB): 224.

PRODUCTION EXAMPLE 8

Production of 3-[N-(2-chlorobenzyl)acetylamino]-4-nitrobenzamide

3- [N-(2-chlorobenzyl)acetylamino]-4-nitrobenzamide was produced from the compound in the same manner as in Production Example 7.

Properties of the compound:

^{1}H-NMR (DMSO-d6, δ): 1.86 (3H, s), 4.64 (1H, d, J=15 Hz), 5.06 (1H, d, J=15 Hz), 7.22–7.40 (4H, m), 7.73 (1H, br s), 7.84 (1H, d, J=2 Hz), 8.03 (1H, dd, J=9, 2 Hz), 8.14 (1H, d, J=9 Hz), 8.22 (1H, br s).

PRODUCTION EXAMPLE 9

Production of 3-[N-(2-chlorobenzyl)acetylamino]-4-nitrobenznitrile

Thirty milliliters of 1,4-dioxane were added dropwise to a solution of 1.70 ml of titanium tetrachloride in 4 ml of dichloromethane in a nitrogen atmosphere while being cooled with ice. Then, a solution of 2.70 g of 3-[N-(2-chlorobenzyl)acetylamino]-4-nitrobenzamide in 65 ml of 1,4-dioxane was added dropwise thereto. After the mixture was stirred for 15 minutes, 3.14 g of triethylamine were added thereto, and the mixture was stirred for 2 hours while being cooled with ice. After the completion of the reaction, the solvent was distilled off under reduced pressure, and the residue was extracted with ethyl acetate and with water. The organic layer was washed with water, and was dried over magnesium sulfate. Subsequently, the solvent was distilled off under reduced pressure. The residue was purified through column chromatography (200 ml, a mixture of n-hexane and ethyl acetate at a ratio of 4:1] to give 1.21 g of 3-[N-(2-chlorobenzyl)acetylamino]-4-nitrobenznitrile.

Properties of the compound:

^{1}H-NMR ($CDCl_3$, δ): 1.92 (3H, s), 4.61 (1H, d, J=15 Hz), 5.40 (1H, d, J=15 Hz), 7.18–7.50 (5H, m), 7.80 (1H, dd, J=9, 2 Hz), 8.01 (1H, d, J=9 Hz) Mass (FAB): 300.

IR (Nujol): 2250 cm^{-1}.

PRODUCTION EXAMPLE 10

Production of 3-[N-(2-chlorobenzyl)amino]-4-nitrobenznitrile

One milliliter of 35% hydrochloric acid was added to a solution of 850 mg of 3-[N-(2-chlorobenzyl)acetylamino]-4-nitrobenzamide in 10 ml of 1,4-dioxane, and the mixture was heat-refluxed for 4 days. After the solvent was distilled off from the reaction solution under reduced pressure, the residue was separated by being poured in a mixture solution of water and chloroform. The organic layer was washed with water, and was dried over magnesium sulfate. The solvent was distilled off under reduced pressure. The residue was purified through column chromatography [50 ml, chloroform] to give 230 mg of 3-[N-(2-chlorobenzyl) amino]-4-nitrobenznitrile.

Properties of the compound:

^{1}H-NMR ($CDCl_3$, δ): 4.65 (2H, d, J=6 Hz), 6.93 (1H, dd, J=9, 2 Hz), 7.10 (1H, d, J=2 Hz), 7.25–7.40 (3H, m), 7.40–7.54 (1H, m), 8.30 (1H, d, J=9 Hz), 8.45 (1H, br s).

Mass (FAB): 258.

IR (Nujol): 2220 cm^{-1}.

PRODUCTION EXAMPLE 11

Production of 4-amino-3-[N-(2-chlorobenzyl) amino]-benznitrile

Fifty milligrams of 10% palladium on carbon were added to a mixed solution of 261 mg of 3-[N-(2-chlorobenzyl) amino]-4-nitrobenznitrile, 15 ml of methanol and 3 ml of 1,4-dioxane to conduct the catalytic reduction in a hydrogen atmosphere at 3 atm. After the completion of the reaction, the reaction solution was filtered through celite, and the filtrate was distilled off under reduced pressure. The resulting solid material was washed with ether, and was collected through filtration to give 196 mg of 4-amino-3-[N-(2-chlorobenzyl)amino]benznitrile.

Properties of the compound:

^{1}H-NMR (DMSO-d6, δ): 4.39 (2H, d, J=5 Hz), 5.57 (1H, t, J=5 Hz), 5.69 (2H, s), 6.46 (1H, d, J=2 Hz), 6.61 (1H, d, J=9 Hz), 6.88 (1H, dd, J=9, 2 Hz), 7.25–7.41 (3H, m), 7.44–7.54 (1H, m).

EXAMPLE 1

Synthesis of 1-(2-bromobenzyl)-6-ethoxycarbonyl-2-n-propylbenzimidazole (42)

A suspension obtained by adding 390 mg of ethyl 3-[N-(2-bromobenzyl)butyrylamino]-4-nitrobenzoate and 210 mg of reduced iron to a mixed solution of 1 ml of acetic acid and 2 ml of ethanol was refluxed for 1 hour while being vigorously stirred. After the completion of the reaction, the reaction solution was cooled down and filtered through celite, and the filtrate was then concentrated under reduced pressure. The residue was separated with the addition of ethyl acetate and a sodium hydrogencarbonate aqueous solution. After the organic solvent layer was dried, the solvent was distilled off under reduced pressure, and the brown residue was obtained. This residue was purified

through flash column chromatography to give 160 mg of yellow crystals of 1-(2-bromobenzyl)-6-ethoxycarbonyl-2-n-propylbenzimidazole (42).

Properties of Compound (42):

^{1}H-NMR ($CDCl_3$, δ): 1.04 (3H, t, J=8 Hz), 1.40 (3H, t, J=8 Hz), 1.78–1.98 (2H, m), 2.34 (2H, t, J=8 Hz), 4.38 (2H, q, J=8 Hz), 5.45 (2H, s), 6.65 (1H, t, J=8 Hz), 7.00 (1H, t, J=8 Hz), 7.13 (1H, t, J=8 Hz), 7.28 (1H, t, J=8 Hz), 7.78 (1H, d, J=10 Hz), 7.99 (1H, d, J=10 Hz), 8.02 (1H, s).

mp: 134–135° C.

EXAMPLE 2

Synthesis of 1-(2-cyanobenzyl)-6-ethoxycarbonyl-2-n-propylbenzimidazole (43)

In the same manner as in Example 1, 160 mg of colorless crystals of 1-(2-cyanobenzyl)-6-ethoxycarbonyl-2-n-propylbenzimidazole (43) were formed from 390 mg of ethyl 3-[N-(2-cyanobenzyl)butyrylamino]-4-nitrobenzoate.

Properties of Compound (43):

^{1}H-NMR ($CDCl_3$, δ): 1.04 (3H, t, J=8 Hz), 1.40 (3H, t, J=8 Hz), 1.88 (2H, sextet, J=8 Hz), 2.80 (2H, t, J=8 Hz), 4.38 (2H, q, J=8 Hz), 5.62 (2H, s), 6.57–6.63 (1H, m), 7.38–7.50 (2H, m), 7.78 (1H, dd, J=1, 8 Hz), 7.79 (1H, d, J=8 Hz), 7.94 (1H, d, J=1 Hz), 8.03 (1H, dd, J=1, 8 Hz).

mp: 132–134° C.

EXAMPLE 3

Synthesis of 1-(2-chlorobenzyl)-6-ethoxycarbonyl-2-phenylbenzimidazole (44)

In the same manner as in Example 1, 220 mg of yellow crystals of 1-(2-chlorobenzyl)-6-ethoxycarbonyl-2-phenylbenzimidazole (44) were obtained from 460 mg of ethyl 3-[N-(2-chlorobenzyl)benzoylamino]-4-nitrobenzoate.

Properties of Compound (44):

^{1}H-NMR ($CDCl_3$, δ): 1.40 (3H, t, J=8 Hz), 4.38 (2H, q, J=8 Hz), 5.56 (2H, s), 6.72 (H, dd, J=1, 8 Hz), 7.18 (1H, dt, J=1, 8 Hz), 7.30 (1H, dt, J=1, 8 Hz), 7.45–7.55 (4H, m), 7.64 (1H, d, J=1Hz), 7.68 (1H, d, J=1 Hz), 7.90 (1H, d, J=10 Hz), 7.95 (1H, s), 8.08 (1H, dd, J=1, 8 Hz).

mp: 140–142° C.

EXAMPLE 4

Synthesis of 6-ethoxycarbonyl-1-(2-fluorobenzyl)-2-n-propylbenzimidazole (45)

In the same manner as in Example 1, 160 mg of colorless crystals of 6-ethoxycarbonyl-1-(2-fluorobenzyl)-2-n-propylbenzimidazole (45) were formed from 390 mg of ethyl 3-[N-(2-fluorobenzyl)butyrylamino]-4-nitrobenzoate.

Properties of Compound (45):

^{1}H-NMR ($CDCl_3$, δ): 1.04 (3H, t, J=8 Hz), 1.40 (3H, t, J=8 Hz), 1.78–1.98 (2H, m), 2.34 (2H, t, J=8 Hz), 4.38 (2H, q, J=8 Hz), 5.45 (2H, s), 6.65 (1H, t, J=8 Hz), 7.00 1H, t, J=8 Hz), 7.13 (1H, t, J=8 Hz), 7.28 (1H, t, J=8 Hz), 7.78 (1H, d, J=10 Hz), 7.99 (1H, d, J=10 Hz), 8.02 (1H, s).

mp: 134–135° C.

EXAMPLE 5

Synthesis of 6-ethoxycarbonyl-1-(4-fluorobenzyl)-2-n-propylbenzimidazole (46)

In the same manner as in Example 1, 160 mg of colorless crystals of 6-ethoxycarbonyl-1-(4-fluorobenzyl)-2-n-propylbenzimidazole (46) were formed from 400 mg of ethyl 3-[N-(4-fluorobenzyl)butyryl)amino]-4-nitrobenzoate.

Properties of Compound (46):

^{1}H-NMR ($CDCl_3$, δ): 1.04 (3H, t, J=8 Hz), 1.40 (3H, t, J=8 Hz), 1.88 (2H, sextet, J=8 Hz), 2.82 (2H, t, J=8 Hz), 4.38 (2H, q, J=8 Hz), 5.38 (2H, s), 7.00 (4H, d, J=7 Hz), 7.77 (1H, d, J=8 Hz), 7.98 (1H, d, J=1 Hz), 8.00 (1H, dd, J=1, 8 Hz).

mp: 134–135° C.

EXAMPLE 6

The following compounds were formed in the same manner as in Example 1.

EXAMPLE 6-1

6-Ethoxycarbonyl-2-n-propyl-1-(2-pyridylmethyl) benzimidazole (47)

Properties of Compound (47)

^{1}H-NMR ($CDCl_3$, δ): 1.03 (3H, t, J=7.5 Hz), 1.39 (3H, t, J=7.5 Hz), 1.89 (2H, m), 2.86 (2H, t, J=7.5 Hz), 4.38 (2H, q, J=7.5 Hz), 5.50 (2H, s), 6.72 (1H, d, J=7.5 Hz), 7.24 (1H, m), 7.58 (1H, dt, J=7.5,1.5 Hz), 7.79 (1H, d, J=7.5 Hz), 7.96–8.02 (2H, m), 8.60 (1H, d, J=4 Hz).

mp: 84–85° C.

EXAMPLE 6-2

6-Ethoxycarbonyl-1-(3-fluorobenzyl)-2-n-propylbenzimidazole (48)

Properties of Compound (48)

^{1}H-NMR ($CDCl_3$, δ): 1.04 (3H, t, J=7.5 Hz), 1.39 (3H, t, J=7.5 Hz), 1.90 (2H, m), 2.81 (2H, t, J=7.5 Hz), 4.39 (2H, q, J=7.5 Hz), 5.39 (2H, s), 6.70–6.84 (2H, m), 7.00 (1H, dt, J=8.5 and 1.5 Hz), 7.78 (1H, d, J=8.5 Hz), 7.96 (1H, s), 8.00 (1H, d, J=8.5 Hz).

mp: 142–146° C.

EXAMPLE 6-3

1-(2,6-Dichlorobenzyl)-6-ethoxycarbonyl-2-n-propylbenzimidazole (49)

Properties of Compound (49)

^{1}H-NMR ($CDCl_3$, δ): 1.03 (3H, t, J=7.5 Hz), 1.38 (3H, t, J=7.5 Hz), 1.88 (2H, m), 2.93 (2H, t, J=7.5 Hz), 4.34 (2H, q, J=7.5 Hz), 5.61 (2H, s), 7.26 (1H, d, J=7.5 Hz), 7.39 (2H, d, J=7.5 Hz), 7.68 (1H, d, J=7.5 Hz), 7.84 (1H, d, J=1.5 Hz), 7.91 (2H, d, J=7.5 Hz).

mp: 153–156° C.

EXAMPLE 6-4

1-(3-Methylbenzyl)-6-ethoxycarbonyl-2-n-propylbenzimidazole (50)

Properties of Compound (50):

colorless solid.

^{1}H-NMR ($CDCl_3$, δ): 1.02 (3H, t, J=7.5 Hz), 1.41 (3H, t, J=7.5 Hz), 1.89 (2H, m), 2.29 (3H, s), 2.82 (2H, t, J=7.5 Hz), 4.38 (2H, q, J=7.5 Hz), 5.35 (2H, s), 6.79–6.86 (2H, m), 7.09 (1H, d, J=7.5 Hz), 7.20 (1H, t, J=7.5 Hz), 7.76 (1H, d, J=7.5 Hz), 7.95–8.02 (2H, m).

EXAMPLE 6-5

2-Cyclopropyl-6-ethoxycarbonyl-1-(2-fluorobenzyl) benzimidazole (51)

Properties of Compound (51):

^{1}H-NMR ($CDCl_3$, δ): 1.10 (2H, m), 1.27 (2H, m), 1.40 (3H, t, J=7.5 Hz), 1.95 (1H, m), 4.37 (2H, q, J=7.5 Hz), 5.56 (2H, s), 6.77 (1H, t, J=7.5 Hz), 7.03 (1H, t, J=7.5 Hz), 7.13 (1H, t, J=7.5 Hz), 7.29 (1H, m), 7.69 (1H, d, J=7.5 Hz), 7.96 (1H, d, J=7.5 Hz), 8.02 (1H, d, J=2 Hz).

mp: 122–126° C.

EXAMPLE 6-6

1-(2-Chlorobenzyl)-6-cyano-2-cyclopropylbenzimidazole (52)

Properties of Compound (52):

^{1}H-NMR ($CDCl_3$, δ): 1.04–1.24 (2H, m), 1.24–1.39 (2H, m), 1.83–2.01 (1H, m), 5.58 (2H, s), 6.54 (1H, d, J=9 Hz), 7.16 (1H, td, J=9, 2 Hz), 7.22–7.38 (1H, m), 7.43–7.56 (3H, m), 7.74 (1H, dd, J=9, 2 Hz).

Mass (FAB): 308 (M+1).

IR (Nujol): 2210 cm^{-1}.

EXAMPLE 6-7

1-(2-Chlorobenzyl)-2-cyclobutyl-6-ethoxycarbonylbenzimidazole (53)

Properties of Compound (53):

^{1}H-NMR ($CDCl_3$, δ): 1.38 (3H, t, J=7.5 Hz), 1.90–2.21 (2H, m), 2.21–2.24 (2H, m), 2.46–2.70 (2H, m), 3.52–3.73 (1H, m), 4.37 (2H, q, J=7.5 Hz), 5.39 (2H, s), 6.34 (1H, dd, J=9, 2 Hz), 7.06 (1H, td, J=9, 2 Hz), 7.23 (1H, td, J=9, 2 Hz), 7.46 (1H, dd, J=9, 2 Hz), 7.83 (1H, d, J=9 Hz), 7.92 (1H, d, J=2 Hz), 8.01 (1H, dd, J=9, 2 Hz).

mp: 111–113° C.

EXAMPLE 6-8

1-(2-Chlorobenzyl)-6-ethoxycarbonyl-2-n-pentylbenzimidazole (54)

Properties of Compound (54):

^{1}H-NMR ($CDCl_3$, δ): 0.87 (3H, t, J=7.5 Hz), 1.22–1.47 (7H, m), 1.74–1.93 (2H, m), 2.80 (2H, t, J=7.5 Hz), 4.37 (2H, q, J=7.5 Hz), 5.47 (2H, s), 6.39 (1H, dd, J=9, 2 Hz), 7.08 (1H, td, J=9, 2 Hz), 7.19–7.33 (1H, m), 7.48 (1H, dd, J=9, 2 Hz), 7.79 (1H, d, J=9 Hz), 7.94 (1H, d, J=2 Hz), 8.00 (1H,dd, J=9, 2 Hz).

EXAMPLE 7

5-Carboxy-1-(2-chlorobenzyl)-2-n-propylbenzimidazole (55)

Twenty milliliters of ethanol and 10.4 g of a 10% sodium hydroxide aqueous solution were added to 2.8 g of 1-(2-chlorobenzyl)-5-ethoxycarbonyl-2-n-propylbenzimidazole, and the mixture was heat-refluxed for 4 hours. The reaction solution was cooled, and was then adjusted to a pH of 6 with 10% hydrochloric acid. The crystals were collected, washed with water, and dried under reduced pressure to give 2.46 g of a colorless solid of 5-carboxy-1-(2-chlorobenzyl)-2-n-propylbenzimidazole (55).

Properties of Compound (55):

^{1}H-NMR (DMSO-d6, δ): 0.93 (3H, t, J=7.5 Hz), 1.75 (2H, m), 2.79 (2H,t, J=7.5 Hz), 5.61 (2H, s), 6.49 (1H, d, J=7.5 Hz), 7.21 (1H, t, J=7.5 Hz),7.33 (1H, t, J=7.5 Hz), 7.46 (1H, d, J=7.5 Hz), 7.56 (1H, d, J=7.5 Hz), 7.80 (1H, d, J=7.5 Hz), 8.20 (1H, s).

EXAMPLE 8

The following compounds were formed in the same manner as in Example 7.

EXAMPLE 8-1

6-Carboxy-1-(3-methylbenzyl)-2-n-propylbenzimidazole (56)

Properties of Compound (56):

colorless solid.

^{1}H-NMR (DMSO-d6, δ): 0.97 (3H, t, J=7.5 Hz), 1.78 (2H, m), 2.23 (3H, s), 3.86 (2H, q, J=7.5 Hz), 5.53 (2H, s), 6.80 (1H, d, J=7.5 Hz), 6.91 (1H,s), 7.07 (1H, d, J=7.5 Hz), 7.21 (1H, t, J=7.5 Hz), 7.65 (1H, d, J=7.5 Hz), 7.79 (1H, d, J=7.5 Hz), 8.04 (1H, s).

EXAMPLE 8-2

2-n-Butyl-7-carboxy-1-(2-chlorobenzyl) benzimidazole (57)

Properties of Compound (57):

^{1}H-NMR (DMSO-d6, δ): 0.84 (3H, t, J=7.5 Hz), 1.34 (2H, m), 1.71 (2H, m), 2.80 (2H, t, J=7.5 Hz), 5.89 (2H, s), 6.03 (1H, d, J=7.5 Hz), 7.13 (1H, t, J=7.5 Hz), 7.27 (2H, t, J=7.5 Hz), 7.48 (1H, d, J=7.5 Hz), 7.63 (1H, d, J=7.5 Hz), 7.87 (1H, d, J=7.5 Hz).

EXAMPLE 8-3

6-Carboxy-2-cyclopropyl-1-(2-fluorobenzyl) benzimidazole (58)

Properties of Compound (58):

^{1}H-NMR (DMSO-d6, δ): 1.04–1.19 (4H, m), 2.37 (1H, m), 5.79 (2H, s), 7.00 (1H, t, J=7.5 Hz), 7.15 (1H, t, J=7.5 Hz), 7.27 (1H, t, J=10.5 Hz), 7.37 (1H, m), 7.60 (1H, d, J=7.5 Hz), 7.82 (1H, d, J=7.5 Hz), 8.11 (1H, s).

mp: 224–229° C.

EXAMPLE 8-4

2-n-Butyl-6-carboxy-1-(2-fluorobenzyl) benzimidazole (59)

Properties of Compound (59):

^{1}H-NMR (DMSO-d6, δ): 0.87 (3H, t, J=7.5 Hz), 1.26–1.48 (2H, m), 1.60–1.80 (2H, m), 2.90 (2H, t, J=7.5 Hz), 5.63 (2H, s), 6.89 (1H, td, J=9, 2 Hz), 7.13 (1H, td, J=9, 2 Hz), 7.20–7.44 (2H, m), 7.64 (1H, d, J=9 Hz), 7.80 (1H, dd, J=9, 2 Hz), 8.08 (1H, d, J=2 Hz).

mp: 216–219° C.

EXAMPLE 9

Synthesis of 1-(2-chlorobenzyl)-6-chlorocarbonyl-2-cyclopropylbenzimidazole hydrochloride (60)

Oxalyl chloride (0.208 ml) was added dropwise to a suspension prepared by adding 390 mg of 6-carboxy-1-(2-chlorobenzyl)-2-cyclopropylbenzimidazole to 10 ml of methylene chloride containing 1 drop of N,N-dimethylformamide at room temperature over a period of several minutes. The mixture was stirred at the same tem-

perature for 2 hours, and was then concentrated under reduced pressure. Isopropyl ether was added to the residue, and the mixture was pulverized to give 450 mg of 1-(2-chlorobenzyl)-6-chlorocarbonyl-2-cyclopropylbenzimidazole hydrochloride (60) as a white powder. Since this product was unstable, it was used as a starting material in the subsequent step without being purified.

EXAMPLE 10

Synthesis of 1-(2-chlorobenzyl)-6-(4-dimethylaminophenylmethylcarbamoyl)-2-n-propylbenzimidazole (61)

Four-hundred milligrams of 6-carboxy-1-(2-chlorobenzyl)-2-n-propylbenzimidazole were dissolved in 3 ml of methylene chloride containing 1 drop of N,N-dimethylformamide. Oxalyl chloride (28 mg) was added to this solution at 5° C. The thus-obtained solution was stirred at room temperature for 1 hour, and was then concentrated under reduced pressure. The residue was dissolved in 3 ml of methylene chloride, and the mixture was added to a mixed solution prepared by adding 271 mg of 4-dimethylaminobenzylamine hydrochloride and 1 ml of triethylamine to 10 ml of methylene chloride at room temperature. The resulting reaction mixture was stirred at the same temperature for 1 hour, washed with water, dried and then concentrated under reduced pressure. The residue was developed and purified through thin-layer chromatography to give 215 mg of 1-(2-chlorobenzyl)-6-(4-dimethylaminophenylmethylcarbamoyl)-2-n-propylbenzimidazole (61).

Properties of Compound (61):

colorless crystal.

^{1}H-NMR ($CDCl_3$, δ): 1.01 (3H, t, J=7 Hz), 1.88 (2H, sextet, J=7 Hz), 2.76 (2H, t, J=7 Hz), 2.95 (6H, s), 4.50 (2H, d, J=5 Hz), 5.45 (2H, s), 6.32 (1H, d, J=5 Hz), 6.36 (1H, d, J=7 Hz), 6.72 (2H, d, J=10 Hz), 7.07 (1H, dt, J=1, 8 Hz), 7.20–7.25 (3H, m), 7.46 (1H, dd, J=1, 8 Hz), 7.58 (1H, dd, J=1, 8 Hz), 7.76 (1H, d, J=8 Hz), 7.82 (1H, d, J=1Hz).

mp: 155–156° C.

EXAMPLE 11

Synthesis of 1-(2-chlorobenzyl)-6-morpholino-carbamoyl-2-n-propylbenzimidazole (62)

In the same manner as in Example 10, 205 mg of 1-(2-chlorobenzyl)-6-morpholinocarbamoyl-2-n-propylbenzimidazole (62) were formed from 200 mg of 6-carboxy-1-(2-chlorobenzyl)-2-n-propylbenzimidazole and 124 mg of 4-aminomorpholine.

Properties of Compound (62):

colorless crystal.

^{1}H-NMR ($CDCl_3$, δ): 1.03 (3H, t, J=8 Hz), 1.88 (2H, sextet, J=8 Hz), 2.62 (4H, bs), 2.72 (2H, t, J=8 Hz), 3.85 (4H, bs), 5.42 (2H, s), 6.42 (1H, dd, J=1, 8 Hz), 7.08 (1H, dt, J=1, 8 Hz), 7.20– 7.28 (3H, m), 7.47 (1H, dd, J=1, 8 Hz), 7.78 (1H, dd, J=1, 8 Hz).

mp: 195–197° C.

EXAMPLE 12

Synthesis of 1-(2-chlorobenzyl)-2-n-propyl-6-thiomorpholinocarbonylbenzimidazole (63)

In the same manner as in Example 10, 160 mg of 1-(2-chlorobenzyl-2-n-propyl-6-thiomorpholinocarbonyl-benzimidazole (63) were formed from 200 mg of 6-carboxy-1-(2-chlorobenzyl)-2-n-propylbenzimidazole and 125 mg of thiomorpholine.

Properties of Compound (63):

colorless crystal.

^{1}H-NMR ($CDCl_3$, δ): 1.03 (3H, t, J=8 Hz), 1.88 (2H, sextet, J=8 Hz), 2.78 (2H, t, J=8 Hz), 2.96 (4H, bt, J=5 Hz), 3.88 (4H, bt, J=5 Hz), 5.46 (2H, s), 6.34 (1H, dd, J=1, 8 Hz), 7.08 (1H, dt, J=1, 8 Hz), 7.26 (2H, dt, J=1, 8 Hz), 7.47 (1H, dd, J=1, 8 Hz), 7.58 (1H, bd, J=8 Hz), 7.76 (1H, s), 7.78 (1H, d, J=8 Hz).

mp: 160–162° C.

EXAMPLE 13

Synthesis of 2-n-butyl-1-(2-chlorobenzyl)-6-[(2-pyridylmethyl)carbamoyl]benzimidazole (64)

In the same manner as in Example 10, 230 mg of 2-n-butyl-1-(2-chlorobenzyl)-6-[(2-pyridylmethyl) carbamoyl]benzimidazole (64) were formed from 200 mg of 6-carboxy-2-n-butyl-1-(2-chlorobenzyl)-benzimidazole and 126 mg of 2-aminomethylpyridine.

Properties of Compound (64):

colorless crystal.

^{1}H-NMR ($CDCl_3$, δ): 0.92 (3H, t, J=8 Hz), 1.42 (2H, sextet, J=8 Hz), 1.82 (2H, quintet, J=8 Hz), 2.82 (2H, t, J=8 Hz), 4.76 (1H, d, J=5 Hz), 5.46 (2H, s), 6.38 (1H, dd, J=1, 8 Hz), 7.08 (1H, dt, J=1, 8 Hz), 7.18–7.26 (2H, m), 7.32 (1H, d, J=8 Hz), 7.46 (1H, dd, J=1, 8 Hz), 7.62 (1H, dt, J=1, 8 Hz), 7.72 (1H, dt, J=1, 8 Hz), 7.82 (1H, d, J=8 Hz), 7.88 (1H, d, J=1Hz), 8.56 (1H, dd, J=1, 8 Hz).

mp: 175–176° C.

EXAMPLE 14

Synthesis of 2-n-butyl-5-carbamoyl-1-(2-chlorobenzyl)benzimidazole (65)

In the same manner as in Example 10, 170 mg of 2-n-butyl-5-carbamoyl-1-(2-chlorobenzyl)benzimidazole (65) were formed from 100 mg of 2-n-butyl-1-(2-chlorobenzyl)-5-carboxybenzimidazole.

Properties of Compound (65):

colorless crystal.

^{1}H-NMR (DMSO-d6, δ): 0.84 (3H, t, J=8 Hz), 1.35 (2H, sextet, J=8 Hz), 1.68 (2H, quintet, J=8 Hz), 2.78 (2H, t, J=8 Hz), 5.58 (2H, s), 6.50 (1H, dd, J=1, 8 Hz), 7.25 (1H, dt, J=1, 8 Hz), 7.28 (1H, bs), 7.35 (1H, dt, J=1, 8 Hz), 7.42 (1H, d, J=10 Hz), 7.56 (1H, dd, J=1, 8 Hz), 7.74 (1H, dd, J=1, 10 Hz), 7.96 (1H, bs), 8.20 (1H, d, J=1Hz).

mp: 195–198° C.

EXAMPLE 15

Synthesis of 1-(2-chlorobenzyl)-2-cyclopropyl-6-morpholinocarbonylbenzimidazole (66)

1-(2-Chlorobenzyl)-6-chlorocarbonyl-2-cyclopropylbenzimidazole hydrochloride (140 mg) was added to a solution prepared by adding 298 mg of morpholine (30% methanol solution) to 10 ml of methylene chloride at room temperature. The reaction mixture was stirred at the same temperature for 1 hour, then washed with water, dried, and concentrated under reduced pressure. The residue was recrystallized with ether to give 20 mg of 1-(2-chlorobenzyl)-2-cyclopropyl-6-morpholinocarbonylbenzimidazole (66).

Properties of Compound (66):

colorless crystal.

^{1}H-NMR ($CDCl_3$, δ): 1.04–1.12 (2H, m), 1.25–1.32 (2H, m), 1.82–1.96 (1H, m), 3.68 (8H, bs), 5.56 (2H, s), 6.55 (1H, dd, J=1, 8 Hz), 7.13 (1H, dt, J=1, 8 Hz), 7.22–7.29 (2H, m), 7.30 (1H, d, J=1Hz), 7.46 (1H, dd, J=1, 8 Hz), 7.77 (1H, d, J=8 Hz).

mp: 193–195° C.

EXAMPLE 16

Synthesis of 1-(2-chlorobenzyl)-2-cyclopropyl-6-[(2-pyridylmethyl)carbamoyl]benzimidazole (67)

In the same manner as in Example 15, 95 mg of 1-(2-chlorobenzyl)-2-cyclopropyl-6-[(2-pyridylmethyl) carbamoyl]benzimidazole (67) were formed from 150 mg of 1-(2-chlorobenzyl)-6-chlorocarbonyl-2-cyclopropylbenzimidazole hydrochloride and 85 mg of 2-aminomethylpyridine.

Properties of Compound (67):

colorless crystal.

^{1}H-NMR ($CDCl_3$, δ): 1.02–1.13 (2H, m), 1.24–1.32 (2H, m), 1.82–1.95 (1H, m), 4.76 (2H, d, J=5 Hz), 5.59 (2H, s), 7.11 (1H, dt, J=1, 8 Hz), 7.20–7.26 (2H, m), 7.34 (1H, d, J=8 Hz), 7.46 (1H, dd, J=1, 8 Hz), 7.60 (1H, t, J=5 Hz), 7.66 (1H, dd, J=1, 8 Hz), 7.73 (1H, s), 7.88 (1H, s).

mp: 134–135° C.

EXAMPLE 17

The following compounds were formed in the same manner as in Example 15.

EXAMPLE 17-1

1-(2-Chlorobenzyl)-2-cyclopropyl-6-(2-pyridylcarbamoyl)benzimidazole (68)

Properties of Compound (68):

^{1}H-NMR ($CDCl_3$, δ): 1.16 (2H, m), 1.32 (2H, m), 1.92 (1H, m), 5.61 (2H, s), 6.57 (1H, d, J=7.5 and 1.5 Hz), 7.15 (1H, dt, J=7.5 and 1.5 Hz), 7.22–7.31 (2H, m), 7.48 (1H, dd, J=7.5 and 1.5 Hz), 7.77 (1H, d, J=9 Hz), 8.05 (2H, m).

mp: 206–209° C.

EXAMPLE 17-2

6-(2-Carboxy-1-pyrrolidinocarbonyl)-1-(2-chlorobenzyl)-2-n-propylbenzimidazole (69)

Properties of Compound (69):

^{1}H-NMR (DMSO-d6, δ): 0.92 (3H, t, J=7.5 Hz), 1.65–1.99 (5H, m), 2.25 (1H, m), 2.77 (2H, t, J=7.5 Hz), 3.50 (2H, m), 4.40 (1H, m), 5.52 (2H, s), 6.53 (1H, d, J=7.5 Hz), 7.21–7.71 (6H, m).

mp: 96° C.

EXAMPLE 17-3

1-(2-Chlorobenzyl)-2-cyclobutyl-6-[(2-pyridylmethyl)carbamoyl]benzimidazole (70)

Properties of Compound (70):

^{1}H -NMR ($CDCl_3$, δ): 1.90–2.21 (2H, m), 2.25–2.37 (2H, m), 2.40–2.65 (2H, m), 3.64 (1H, m), 4.76 (2H, d, J=5 Hz), 5.39 (2H, s), 6.33 (1H, d, J=7.5 Hz), 7.05 (1H, t, J=7.5 Hz), 7.16–7.26 (2H, m), 7.33 (1H, d, J=7.5 Hz), 7.46 (1H, d, J=7.5 Hz), 7.69–7.76 (3H, m), 7.73 (1H, d, J=7.5 Hz), 7.86 (1H, s), 8.55 (1H, d, J=5 Hz).

mp: 183–185° C.

EXAMPLE 17-4

(1-(2-Chlorobenzyl)-2-n-propyl-5-[(2-pyridylmethyl)carbamoyl]benzimidazole (71)

Properties of Compound (71)

^{1}H-NMR ($CDCl_3$, δ): 1.03 (3H, t, J=7.5 Hz), 1.90 (2H, m), 2.80 (2H, t, J=7.5 Hz), 4.80 (2H, d, J=5 Hz), 5.44 (2H, s), 6.40 (1H, d, J=7.5 Hz), 7.09 (1H, t, J=7.5 Hz), 7.21–7.27 (3H, m), 7.34 (1H, d, J=7.5 Hz), 7.47 (1H, d, J=7.5 Hz), 7.64–7.72 (2H, m), 7.83 (1H, dd, J=7.5 and 2 Hz), 8.30 (1H, d, J=2 Hz), 8.56 (1H, d, J=5 Hz).

mp: 115–116° C.

EXAMPLE 17-5

1-(2-Chlorobenzyl)-6-[N-methyl-N-(2-pyridylmethyl)carbamoyl]-2-n-propylbenzimidazole (72)

Properties of Compound (72):

^{1}H -NMR (DMSO-d6, δ): 1.03 (3H, t, J=7.5 Hz), 1.87 (2H, m), 2.79 (2H, t, J=7.5 Hz), 3.05 (3H, brs), 4.60 (1H, brs), 4.87 (1H, brs), 5.40 (2H, d, J=unknown), 6.38 (1H, d, J=unknown), 7.05 (1H, brs), 7.20 (3H, m), 7.35–7.49 (3H, m), 7.60–7.81 (2H, m), 8.54 (1H, brs).

mp: 99° C.

EXAMPLE 17-6

1-(2-Chlorobenzyl)-6-piperonylcarbamoyl-2-n-propylbenzimidazole (73)

Properties of Compound (73):

^{1}H -NMR ($CDCl_3$, δ): 1.01 (3H, t, J=7.5 Hz), 1.88 (2H, m), 2.78 (2H, t, J=7.5 Hz), 4.54 (2H, d, J=5 Hz), 5.45 (2H, s), 5.95 (2H, s), 6.36 (1H, d, J=7.5 Hz), 6.44 (1H, t, J=5 Hz), 6.75–6.85 (3H, m), 7.08 (1H, t, J=7.5 Hz), 7.23 (1H, t, J=7.5 Hz), 7.45 (1H, d, J=7.5 Hz), 7.67 (1H, dd, J=7.5, 2 Hz), 7.78 (1H, d, J=7.5 Hz), 7.83 (1H, s).

mp: 131–134° C.

EXAMPLE 17-7

1-(2-chlorobenzyl)-6-phenylcarbamoyl-2-n-propylbenzimidazole (74)

Properties of Compound (74):

^{1}H-NMR ($CDCl_3$, δ): 1.03 (3H, t, J=7.5 Hz), 1.90 (2H, m), 2.81 (2H, t, J=7.5 Hz), 5.47 (2H, s), 6.40 (1H, d, J=7.5 Hz), 7.06–7.18 (2H, m), 7.26 (1H, t, J=7.5 Hz), 7.35 (2H, t, J=7.5 Hz), 7.48 (1H, d, J=7.5 Hz), 7.64 (2H, d, J=7.5 Hz), 7.72 (1H, dd, J=7.5 and 2 Hz), 7.85–7.95 (3H, m).

mp: 168° C.

EXAMPLE 17-8

1-(2-Chlorobenzyl)-2-n-propyl-6-[(4-pyridylmethyl) carbamoyl]benzimidazole (75)

Properties of Compound (75):

^{1}H-NMR (DMSO-d6, δ): 0.93 (3H, t, J=7.5 Hz), 1.76 (2H, m), 2.78 (2H, t, J=7.5 Hz), 4.49 (2H, d, J=5 Hz), 6.42 (1H, d, J=7.5 Hz), 7.22 (1H, t, J=7.5 Hz), 7.27 (2H, d, J=7.5 Hz),

7.34 (1H, t, J=7.5 Hz), 7.57 (1H, d, J=7.5 Hz), 7.69 (1H, d, J=7.5 Hz), 7.80 (1H, d, J=7.5 Hz), 7.97 (1H, s), 8.48 (2H, d, J=7.5 Hz), 9.03 (1H, t, J=5 Hz).

mp: 170–173° C.

EXAMPLE 17-9

1-(2-Chlorobenzyl)-2-n-propyl-6-[(3-pyridylmethyl) carbamoyl]benzimidazole (76)

Properties of Compound (76):

^{1}H-NMR (DMSO-d6, δ): 0.95 (3H, t, J=7.5 Hz), 1.76 (2H, m), 2.80 (2H, t, J=7.5 Hz), 4.50 (2H, d, J=5 Hz), 5.60 (2H, s), 6.42 (1H, d, J=7.5 Hz), 7.23 (1H, t, J=7.5 Hz), 7.30–7.58 (2H, m), 7.57 (1H, d, J=7.5 Hz), 7.67–7.74 (2H, m), 7.75 (1H, d, J=7.5 Hz), 7.97 (1H, s), 8.46 (1H, d, J=5 Hz), 8.56 (1H, s), 9.0 (1H, t, J=5 Hz).

mp: 193–195° C.

EXAMPLE 17-10

1-(2-Chlorobenzyl)-6-[N-methyl-N-(2-pyridyl) carbamoyl]-2-n-propylbenzimidazole (77)

Properties of Compound (77):

^{1}H-NMR (DMSO-d6, δ): 0.90 (3H, t, J=7.5 Hz), 1.70 (2H, m), 2.73 (2H, t, J=7.5 Hz), 3.40 (3H, s), 5.42 (2H, s), 6.23 (1H, d, J=7.5 Hz), 6.91 (1H, d, J=7.5 Hz), 6.98 (1H, m), 7.15–7.25 (3H, m), 7.36 (1H, t, J=7.5 Hz), 7.46–7.57 (3H, m), 8.23 (1H, m).

mp: 143–146° C.

EXAMPLE 17-11

1-(2-Chlorobenzyl)-6-(homopiperidinocarbonyl)-2-n-propylbenzimidazole (78)

Properties of Compound (78):

^{1}H-NMR ($CDCl_3$, δ): 1.03 (3H, t, J=7.5 Hz), 1.46–1.94 (10H, m), 2.80 (2H, t, J=7.5 Hz), 3.32 (2H, brs), 3.64 (2H, t, J=7.5 Hz), 5.41 (2H, s), 6.42 (1H, d, J=7.5 Hz), 7.07 (1H, t, J=7.5 Hz), 7.19–7.29 (3H, m), 7.45 (1H, d, J=7.5 Hz), 7.76 (1H, d, J=7.5 Hz).

mp: 136–137° C.

EXAMPLE 17-12

1-(3-Methylbenzyl)-2-n-propyl-6-[(2-pyridylmethyl) carbamoyl]benzimidazole (79)

Properties of Compound (79):

^{1}H-NMR ($CDCl_3$, δ): 1.02 (3H, t, J=7.5 Hz), 1.88 (2H, m), 2.26 (3H, s), 2.81 (2H, t, J=7.5 Hz), 4.76 (2H, d, J=5 Hz), 5.36 (2H, s), 6.78–6.84 (2H, m), 7.07 (1H, d, J=7.5 Hz), 7.13–7.22 (2H, m), 7.33 (1H, d, J=7.5 Hz), 7.57–7.72 (2H, m), 7.78 (1H, d, J=7.5 Hz), 7.94 (1H, s), 8.55 (1H, d, J=5 Hz).

mp: 129–131° C.

EXAMPLE 17-13

2-n-Butyl-1-(2-fluorobenzyl)-6-[N-methyl-N-(2-pyridylmethyl)carbamoyl]benzimidazole (80)

Properties of Compound (80):

^{1}H-NMR ($CDCl_3$, δ): 0.92 (3H, t, J=7.5 Hz), 1.45 (2H, m), 1.83 (2H, m), 2.86 (2H, t, J=7.5 Hz), 3.06 (3H, brs), 4.61 (1H, brs), 4.86 (1H, brs), 5.37 (2H, brd), 6.62 (1H, brd), 6.97 (1H, brs), 7.07–7.85 (8H, m), 8.57 (1H, d, J=5 Hz).

mp: 97–100° C.

EXAMPLE 17-14

1-(2-Chlorobenzyl)-2-ethyl-6-[(2-pyridylmethyl) carbamoyl]benzimidazole (81)

Properties of Compound (81):

^{1}H-NMR ($CDCl_3$, δ): 1.43 (3H, t, J=7.5 Hz), 2.84 (2H, q, J=7.5 Hz), 4.76 (2H, d, J=5 Hz), 5.45 (2H, s), 6.37 (1H, d, J=7.5 Hz), 7.07 (1H, t, J=7.5 Hz), 7.19–7.28 (2H, m), 7.33 (1H, d, J=7.5 Hz), 7.45 (1H, dd, J=7.5 and 2 Hz), 7.62–7.75 (3H, m), 7.82 (1H, d, J=7.5 Hz), 7.89 (1H, d, J=2 Hz), 8.55 (1H, d, J=5 Hz).

mp: 167–168° C.

EXAMPLE 17-15

2-n-Butyl-1-(2-chlorobenzyl)-7-[(2-pyridylmethyl) carbamoyl]benzimidazole (82)

Properties of Compound (82):

^{1}H-NMR ($CDCl_3$, δ): 0.93 (3H, t, J=7.5 Hz), 1.42 (2H, m), 1.83 (2H, m), 2.81 (2H, t, J=7.5 Hz), 4.44 (2H, d, J=5 Hz), 5.70 (2H, s), 6.13 (1H, dd, J=7.5 and 2 Hz), 6.85–6.97 (3H, m), 7.12–7.28 (4H, m), 7.34 (1H, d, J=7.5 Hz), 7.62 (1H, dt, J=7.5 and 2 Hz), 7.88 (1H, d, J=7.5 Hz), 8.40 (1H, d, J=5 Hz).

mp: 112–114° C.

EXAMPLE 17-16

2-Cyclopropyl-1-(2-fluorobenzyl)-6-(piperonylcarbamoyl)benzimidazole (83)

Properties of Compound (83):

^{1}H-NMR (DMSO-d6, δ): 1.05 (4H, m), 2.27 (1H, m), 4.38 (2H, d, J=5 Hz), 5.71 (2H, s), 5.98 (2H, s), 6.73–6.91 (4H, m), 7.14 (1H, t, J=7.5 Hz), 7.27 (1H, t, J=7.5 Hz), 7.36 (1H, m), 7.55 (1H, d, J=7.5 Hz), 7.73 (1H, dd, J=7.5 and 2 Hz), 8.04 (1H, s), 8.87 (1H, t, J=5 Hz).

mp: 170–173° C.

EXAMPLE 17-17

2-[[1-(2-chlorobenzyl)-2-ethylbenzimidazol-6-yl] carbonylaminomethyl]-pyridine-1-oxide (84)

Properties of Compound (84):

^{1}H-NMR ($CDCl_3$, δ): 1.42 (3H, t, J=7.5 Hz), 2.82 (2H, q, J=7.5 Hz), 4.81 (2H, d, J=7.5 Hz), 5.43 (2H, s), 6.31 (1H, d, J=7.5 Hz), 7.06 (1H, t, J=7.5 Hz), 7.20–7.31 (3H, m), 7.44 (1H, d, J=7.5 Hz), 7.52 (1H, dd, J=7.5 and 2 Hz), 7.65 (1H, dd, J=7.5 and 2 Hz), 7.77–7.83 (2H, m), 7.96 (1H, t, J=7.5 Hz), 8.23 (1H, dd, J=7.5 and 2 Hz).

mp: 204–207° C.

EXAMPLE 17-18

2-n-Butyl-1-(2-fluorobenzyl)-6-(2-pyridylmethylcarbamoyl)benzimidazole (85)

Properties of Compound (85):

^{1}H-NMR ($CDCl_3$, δ): 0.92 (3H, t, J=7.5 Hz), 1.38–1.49 (2H, m), 1.77–1.88 (2H, m), 2.86 (2H, t, J=7.5 Hz), 4.78 (2H, d, J=5 Hz), 5.46 (2H, s), 6.67 (1H, t, J=9 Hz), 7.00 (1H, t, J=9 Hz), 7.13 (1H, t, J=9 Hz), 7.19–7.31 (2H, m), 7.33 (1H, d, J=9 Hz), 7.60 (1H, br peak), 7.65–7.74 (2H, m), 7.79 (1H, d, J=9 Hz), 7.97 (1H, d, J=2 Hz), 8.58 (1H, d, J=5 Hz).

mp: 154–155° C.

EXAMPLE 18

Synthesis of 6-tert-buthoxycabonylamino-1-(2-chlorobenzyl)-2-n-propylbenzimidazole (86)

Two-hundred milligrams of 6-carboxy-1-(2-chlorobenzyl)-2-n-propylbenzimidazole were suspended in 5 ml of tert-butyl alcohol, and 0.19 ml of diphenylphosphorylazide and 0.21 ml of diisopropylethylamine were added thereto at room temperature. The reaction mixture was refluxed for 4 hours, and was then separated with ethyl acetate and with water. The organic layer was washed with water, dried, and then concentrated under reduced pressure. The residue was developed and purified through column chromatography using a mixture of ethyl acetate and hexane (at a ratio of from 1:10 to 1:3), and was further recrystallized from a mixture of ethyl acetate and hexane to give 165 mg of 6-tert-buthoxycabonylamino-1-(2-chlorobenzyl)-2-n-propylbenzimidazole (86).

Properties of Compound (86):

colorless crystal.

^{1}H-NMR ($CDCl_3$, δ): 0.98 (3H, t, J=8 Hz), 1.50 (9H, s), 1.86 (2H, sextet, J=8 Hz), 2.72 (2H, t, J=8 Hz), 5.38 (2H, s), 6.40 (1H, dd, J=1, 8 Hz), 6.95 (1H, dd, J=1, 10 Hz), 7.08 (1H, dt, J=1, 8 Hz), 7.24 (1H, dt, J=1, 8 Hz), 7.28 (1H, d, J=1 Hz), 7.45 (1H, dd, J=1, 8 Hz), 7.66 (1H, d, J=10 Hz).

mp: 166–168° C.

EXAMPLE 19

Synthesis of 1-(2-chlorobenzyl)-6-cyano-2-n-propylbenzimidazole (87)

A solution of 1 mol of titanium tetrachloride in 0.14 ml of dichloromethane and 0.36 ml of triethylamine were added to a solution of 200 mg of 6-carbamoyl-1-(2-chlorobenzyl)-2-n-propylbenzimidazole in 4 ml of tetrahydrofuran at 0° C., and the mixture was stirred at 20° C. for 2 hours. The reaction mixture was separated with ethyl acetate and with water. The organic layer was washed with water, dried, and then concentrated under reduced pressure. The residue was developed and purified through column chromatography using a mixture of ethyl acetate and hexane (at a ratio of from 1:10 to 1:3), and was further recrystallized from a mixture of ethyl acetate and hexane to give 140 mg of 1-(2-chlorobenzyl)-6-cyano-2-n-propylbenzimidazole (87).

Properties of Compound (87):

colorless crystal.

^{1}H-NMR ($CDCl_3$, δ): 1.05 (3H, t, J=8 Hz), 1.90 (2H, sextet, J=8 Hz), 2.85 (2H, t, J=8 Hz), 5.45 (2H, s), 6.42 (1H, dd, J=1, 8 Hz), 7.15 (1H, dt, J=1, 8 Hz), 7.28 (1H, dt, J=1, 8 Hz), 7.48 (1H, s), 7.50 (1H, d, J=10 Hz), 7.54 (1H, dd, J=1, 8 Hz), 7.85 (1H, d, J=10 Hz).

mp: 124–126° C.

EXAMPLE 20

Synthesis of 1-(2-chlorobenzyl)-6-mesylamino-2-n-propylbenzimidazole (88)

1-(2-Chlorobenzyl)-2-n-propylbenzimidazole (150 mg) and 61 mg of triethylamine were dissolved in 3 ml of methylene chloride, and 70 mg of methanesulfonyl chloride were added thereto at room temperature. The mixture was stirred for 1 hour, then washed with dilute hydrochloric acid, washed with water, and dried. The solvent was distilled off under reduced pressure. The residual solid was collected with ether through filtration to give 124 mg of 1-(2-chlorobenzyl)-6-mesylamino-2-n-propylbenzimidazole (88).

Properties of Compound (88):

^{1}H-NMR ($CDCl_3$—CD3OD, δ): 0.94 (3H, t, J=7.5 Hz), 1.76 (2H, m), 2.71 (2H, t, J=7.5 Hz), 2.81 (3H, s), 5.36 (2H, s), 6.40 (1H, d, J=7.5 Hz), 6.98–7.22 (4H, m), 7.40 (1H, d, J=7.5 Hz), 7.59 (1H, d, J=7.5 Hz).

mp: 191–193° C.

EXAMPLE 21

Synthesis of 6-acetylamino-1-(2-chlorobenzyl)-2-n-propylbenzimidazole (89)

Acetic anhydride (62 mg) was added to a solution of 150 mg of 6-amino-1-(2-chlorobenzyl)-2-n-propylbenzimidazole and 61 mg of triethylamine in 3 ml of methylene chloride at room temperature, and the mixture was stirred for 1 hour. The reaction mixture was washed with water, and was then dried. The solvent was distilled off under reduced pressure. The residue was crystallized with ether to give 143 mg of 6-acetylamino-1-(2-chlorobenzyl)-2-n-propylbenzimidazole (89).

Properties of Compound (89):

^{1}H-NMR ($CDCl_3$, δ): 1.00 (3H, t, J=7.5 Hz), 1.86 (2H, m), 2.17 (3H, s), 2.73 (2H, t, J=7.5 Hz), 5.39 (2H, s), 6.43 (1H, d, J=7.5 Hz), 6.98–7.11 (2H, m), 7.22 (1H, t, J=7.5 Hz), 7.45 (1H, d, J=7.5 Hz), 7.59 (1H, brs), 7.68 (1H, d, J=7.5 Hz), 7.84 (1H, d, J=1.5 Hz).

mp: 180–182° C.

EXAMPLE 22

Synthesis of 6-amino-1-(2-chlorobenzyl)-2-n-propylbenzimidazole (90)

Seven-hundred milligrams of 6-tert-butoxycarbonylamino-1-(2-chlorobenzyl)-2-n-propylbenzimidazole were dissolved in a mixed solvent of 10 ml of methylene chloride and 1 ml of trifluoroacetic acid, and the mixture was stirred at room temperature for 5 hours. A small amount of methylene chloride was added to the reaction solution. The mixture was washed with a sodium carbonate aqueous solution, and was dried. The solvent was then distilled off. The residue was crystallized from a mixed solvent of n-hexane and ether to give 455 mg of 6-amino-1-(2-chlorobenzyl)-2-n-propylbenzimidazole (90).

Properties of Compound (90):

^{1}H-NMR ($CDCl_3$, δ): 1.01 (3H, t, J=7.5 Hz), 1.86 (2H, m), 2.73 (2H, t, J=7.5 Hz), 5.30 (2H, s), 6.41 (1H, d, J=1.5 Hz), 6.48 (1H, d, J=7.5 Hz), 6.66 (1H, dd, J=7.5 and 1.5 Hz), 7.10 (1H, t, J=7.5 Hz), 7.25 (1H, t, J=7.5 Hz), 7.46 (1H, d, J=7.5 Hz), 7.57 (1H, d, J=7.5 Hz).

mp: 121–122° C.

EXAMPLE 23

Synthesis of 1-(2-chlorobenzyl)-2-n-propyl-6-ureidobenzimidazole (91)

1-(2-Chlorobenzyl)-2-n-propyl-6-ureidobenzimidazole (91) was formed in the same manner as in Example 21.

Properties of Compound (91):

^{1}H-NMR (DMSO-d6, δ): 0.93 (3H, t, J=7.5 Hz), 1.72 (2H, m), 2.73 (2H, t, J=7.5 Hz), 5.43 (2H, s), 5.73 (2H, s), 6.42

(1H, dd, J=7.5 and 1.5 Hz), 7.05 (1H, dd, J=7.5 and 1.5 Hz), 7.22 (1H, dt, J=7.5 and 1.5 Hz), 7.33 (1H, dt, J=7.5 and 1.5 Hz), 7.45 (1H, d, J=7.5 Hz), 7.50 (1H, s), 7.57 (1H, dd, J=7.5 and 1.5 Hz), 8.50 (1H, s).

mp: 198° C.

PRODUCTION EXAMPLE 12

Production of ethyl 3-acetylamino-4-nitrobenzoate

Nine milliliters of acetyl chloride were added to a mixture of 18.4 g of ethyl 3-amino-4-nitrobenzoate and 200 ml of N,N-dimethylaniline while being cooled with ice. The mixture was stirred at room temperature for 2 hours and then at 50° C. for 2 hours. The reaction solution was poured into cold 1-N hydrochloric acid, and the mixture was extracted twice with ethyl acetate. The organic layer was washed with 1-N hydrochloric acid and then with water, and was dried. The solvent was then distilled off under reduced pressure. The residue was purified through silica-gel column chromatography (eluent: a mixture of ethyl acetate and hexane at a ratio of from 1:10 to 1:4) to give 19.6 g of ethyl 3-acetylamino-4-nitrobenzoate.

Properties of the compound:

^{1}H-NMR($CDCl_3$, δ): 1.42(3H, t, J=7.1 Hz), 2.32(3H, s), 4.43(2H, q, J=7.1 Hz), 7.82(1H, dd, J=1.8 and 8.7 Hz), 8.25(1H, d, J=8.7 Hz), 9.35(1H, d, J=1.8 Hz), 10.19(1H, s).

PRODUCTION EXAMPLE 13

Production of ethyl 4-nitro-3-phenylacetylaminobenzoate

In the same manner as in Production Example 12, 3.30 g of ethyl 4-nitro-3-phenylacetylaminobenzoate were formed from 2.02 g of ethyl 3-amino-4-nitrobenzoate and 1.87 g of phenylacetyl chloride.

Properties of the compound:

^{1}H-NMR($CDCl_3$, δ): 1.41(3H, t, J=7.2 Hz), 3.85(2H, s), 4.42(2H, q, J=7.2 Hz), 7.34–7.49(5H, m), 7.79(1H, m), 8.19(1H, d, J=8.7 Hz), 9.39(1H, d, J=1.6 Hz), 10.15(1H, s).

PRODUCTION EXAMPLE 14

Production of ethyl 3-[N-(2-chlorobenzyl) acetylamino]-4-nitrobenzoate

A solution of 1.706 g of ethyl 3-acetylamino-4-nitrobenzoate in 12 ml of N,N-dimethylformamide were added 0.406 g of 60% sodium hydride while being cooled with ice, and the mixture was stirred at room temperature for 40 minutes. A solution of 1.806 g of 2-chlorobenzyl bromide in 10 ml of N,N-dimethylformamide was added thereto, and the mixture was stirred at room temperature for 3 hours. The reaction mixture was poured into cold 1-N hydrochloric acid, and the mixed solution was extracted twice with ethyl acetate. The organic layer was washed with 1-N hydrochloric acid and then with water, and was dried. The solvent was distilled off under reduced pressure. The residue was purified through silica-gel column chromatography (eluent: a mixture of ethyl acetate and hexane at a ratio of from 1:10 to 1:4) to give 2.08 g of oily ethyl 3-[N-(2-chlorobenzyl) acetylamino]-4-nitrobenzoate.

Properties of the compound:

^{1}H-NMR($CDCl_3$, δ): 1.38(3H, t, J=7.1 Hz), 1.92(3H, s), 4.28–4.45(2H, m), 4.72(1H, d, J=14.5 Hz), 5.34(1H, d, J=14.5 Hz), 7.16–7.44(4H, m), 7.69(1H, d, J=1.7 Hz), 7.94(1H, d, J=8.4 Hz), 8.13(1H, dd, J=1.7 and 8.4 Hz).

PRODUCTION EXAMPLE 15

Production of ethyl 4-nitro-3-[N-[2-(trifluoromethyl)benzyl]acetylamino]benzoate

In the same manner as in Production Example 14, 1.82 g of ethyl 4-nitro-3-[N-[2-(trifluoromethyl)-benzyl] acetylamino]benzoate were formed from 1.49 g of ethyl 3-acetylamino-4-nitrobenzoate and 1.69 g of 2-(trifluoromethyl)benzyl bromide.

Properties of the compound:

^{1}H-NMR($CDCl_3$, δ): 1.37(3H, t, J=7.1 Hz), 1.96(3H, s), 4.29–4.42(2H, m), 4.78(1H, d, J=15.4 Hz), 5.40(1H, d, J=15.4 Hz), 7.38(1H, t, J=7.6 Hz), 7.51–7.58(2H, m), 7.61 (1H, d, J=1.7 Hz), 7.67(1H, d, J=7.8 Hz), 7.92(1H, d, J=8.4 Hz), 8.13(1H, dd, J=1.7 and 8.4 Hz).

mp: 153.5–158.0° C.

PRODUCTION EXAMPLE 16

Production of ethyl 4-nitro-3-[N-[4-(trifluoromethyl)benzyl]acetylaminobenzoate

In the same manner as in Production Example 14, 1.52 g of ethyl 4-nitro-3-[N-[4-(trifluoromethyl)-benzyl] acetylaminobenzoate were formed from 1.50 g of ethyl 3-acetylamino-4-nitrobenzoate and 1.71 g of 4-(trifluoromethyl)benzyl bromide.

Properties of the compound:

^{1}H-NMR($CDCl_3$, δ): 1.36(3H, t, J=7.1 Hz), 1.91(3H, s), 4.32–4.43(2H, m), 4.42(1H, d, J=14.6 Hz), 5.33(1H, d, J=14.6 Hz), 7.30(2H, d, J=8.1 Hz), 7.54(2H, d, J=8.1 Hz), 7.61(1H, d, J=1.8 Hz), 7.96(1H, d, J=8.4 Hz), 8.12(1H, dd, J=1.8 and 8.4 Hz).

PRODUCTION EXAMPLE 17

Production of 2-cyanobenzyl 3-[N-(2-cyanobenzyl) acetylamino]-4-nitrobenzoate

A solution of 1.50 g of 3-acetylamino-4-nitrobenzoic acid in 10 ml of N,N-dimethylformamide was added dropwise to a slurry of 0.802 g of 60% sodium hydride and 10 ml of N,N-dimethylformamide at room temperature, and the mixture was stirred for 30 minutes. Subsequently, a solution of 3.93 g of 2-cyanobenzyl bromide in 10 ml of N,N-dimethylformamide was added dropwise thereto, and the mixture was stirred for 30 minutes. Ethyl acetate was poured into the reaction solution, and the crystals precipitated were separated through filtration. The crystals obtained were washed with ethyl acetate, and were further dissolved in chloroform. The filtrate from which the solid component was removed was concentrated to give 1.96 g of yellow crystals of 2-cyanobenzyl 3-[N-(2-cyanobenzyl) acetylamino]-4-nitrobenzoate.

Properties of the compound:

^{1}H-NMR($CDCl_3$, δ): 1.92(3H, s), 4.92(1H, d, J=4.8 Hz), 5.24(2H, d, J=4.9 Hz), 5.44(2H, dd, J=7.9 and 2.9 Hz), 7.36(1H, t, J=7.5 Hz), 7.47(1H, d, J=7.7 Hz), 7.52(1H, t, J=7.7 Hz), 7.56–7.62(2H, m), 7.63–7.71(2H, m), 7.76(1H, d, J=7.8 Hz), 7.80(1H, d, J=1.7 Hz), 7.99(1H, d, J=8.4 Hz), 8.25(1H, dd, J=8.4 and 1.8 Hz).

PRODUCTION EXAMPLE 18

Production of ethyl 4-amino-3-(N-i-propylbutyrylamino)benzoate

A solution of 2.00 g of ethyl 3-butyrylamino-4-nitrobenzoate in 10 ml of N,N-dimethylformamide was

added dropwise to a slurry of 0.428 g of 60% sodium hydride and 10 ml of N,N-dimethylformamide at room temperature, and the mixture was stirred for 30 minutes. A solution of 1.46 g of isopropyl iodide in 10 ml of N,N-dimethylformamide was then added dropwise thereto, and the mixture was stirred at 100° C. for 5 days. The reaction solution was poured into a mixed solution of 80 g of dilute hydrochloric acid and 80 g of ethyl acetate for separation. The resulting organic layer was washed with 50 g of water, and was then concentrated under reduced pressure. The residue was purified through silica-gel column chromatography (eluent: a mixture of hexane and ethyl acetate at a ratio of 4:1) to obtain 0.260 g of crude ethyl 4-nitro-3-(N-i-propylbutyrylamino)benzoate. Subsequently, 3 ml of ethanol and 2 ml of acetic acid were added to 0.260 g of ethyl 4-nitro-3-(N-i-propylbutyrylamino)benzoate at room temperature, and 0.519 g of reduced iron were further added thereto. The mixture was heat-refluxed for 4 hours. The solid material was removed using a filtration aid, and the filtrate was concentrated. The residue were added 30 ml of ethyl acetate and 30 ml of dilute hydrochloric acid for separation. The organic layer was washed with 30 ml of water, and was then concentrated under reduced pressure. The residue was purified through preparative thin-layer silica-gel chromatography (developing eluent: a mixture of hexane and ethyl acetate at a ratio of 1:1) to give 0.06 g of ethyl 4-amino-3-(N-i-propylbutyrylamino)benzoate.

Properties of the compound:

^{1}H-NMR($CDCl_3$, δ): 0.82(3H, t, J=7.4 Hz), 1.01(3H, d, J=6.9 Hz), 1.24(3H, d, J=6.6 Hz), 1.38(3H, t, J=7.0 Hz), 1.54–1.62(2H, m), 1.87–2.04(2H, m), 4.34(2H, q, J=7.0 Hz), 4.45(2H, s), 4.88–4.96(1H, m), 6.78(1H, d, J=8.4 Hz), 7.64(1H, d, J=1.9 Hz), 7.87(1H, dd; J=8.4 and 1.9 Hz).

PRODUCTION EXAMPLE 19

Production of ethyl 3-nitro-4-phenylacetylaminobenzoate

In the same manner as in Production example 12, 6.00 g of ethyl 3-nitro-4-phenylacetylaminobenzoate were formed from 4.04 g of ethyl 4-amino-3-nitrobenzoate and 3.74 g of phenylacetyl chloride.

PRODUCTION EXAMPLE 20

Production of N-benzenesulfonyl-3-amino-4-nitrobenzamide

N,N'-carbonyldiimidazole (28.9 g) was added to a solution of 20.0 g of 3-acetylamino-4-nitrobenzoic acid in 300 ml of N,N-dimethylformamide, and the mixture was stirred at room temperature for 1 hour. Further, 28.00 g of benzenesulfonamide and 27.16 g of diazabicycloundecene were added thereto, and the mixture was stirred at 100° C. for 4 days. The solvent was distilled off under reduced pressure. Chloroform and a 10% sodium hydroxide aqueous solution were added to the residue, and the mixture was vigorously stirred. The aqueous layer was neutralized with 10% hydrochloric acid, and the mixture was vigorously stirred with the addition of chloroform. The crystals precipitated were separated through filtration, and were dried to 14.4 g of N-benzenesulfonyl-3-amino-4-nitrobenzamide.

Properties of the compound:

^{1}H-NMR(DMSO-d6, δ): 6.93(1H, dd, J=1.8 and 9.0 Hz), 7.43(1H, d, J=1.8 Hz), 7.52(2H, br s), 7.65(2H, t, J=7.5 Hz), 7.74(1H, t, J=7.5 Hz), 7.98–7.82(3H, m), 12.74(1H, s).

PRODUCTION EXAMPLE 21

Production of N-benzenesulfonyl-3-(biphenyl-4-ylmethylamino)-4-nitrobenzamide potassium salt

A solution of 10.0 g of N-benzenesulfonyl-3-amino-4-nitrobenzamide in 150 ml of methanol were added 56.5 g of a 20% potassium hydrogencarbonate aqueous solution and 11.5 g of 4-bromomethylbiphenyl, and the mixture was stirred at 70° C. for 3 hours. The mixture was cooled, and the crystals precipitated were collected through filtration, and were dried to give 4.27 g of N-benzenesulfonyl-3-(biphenyl-4-ylmethylamino)-4-nitrobenzamide potassium salt.

Properties of the compound:

^{1}H-NMR(DMSO-d6, δ): 4.65(2H, d, J=5.8 Hz), 7.19(1H, d, J=8.9 Hz), 7.33–7.42(4H, m), 7.57–7.71(4H, m), 7.75–7.81(2H, m), 8.02(1H, d, J=8.9 Hz), 8.61(1H, br t).

IR(Nujol): 1598 cm^{-1}.

PRODUCTION EXAMPLE 22

Production of N-benzenesulfonyl-4-amino-3-(biphenyl-4-ylmethylamino)benzamide potassium salt

Five-percent palladium on carbon (0.64 g) was added to a mixture containing 4.27 g of N-benzenesulfonyl-3-(biphenyl-4-ylmethylamino)-4-nitrobenzamide potassium salt, 10.7 g of a 20% potassium hydrogencarbonate aqueous solution and 200 ml of methanol, and the mixture was stirred in a hydrogen atmosphere at 35° C. for 14 hours. The crystals precipitated were dissolved in 400 ml of a mixed solution of acetone and water (at a ratio of 5:2). The solid material was separated through filtration. The filtrate was concentrated, and the crystals precipitated were separated through filtration, and were dried to give 3.15 g of N-benzenesulfonyl-4-amino-3-(biphenyl-4-ylmethylamino) benzamide potassium salt.

Properties of the compound:

^{1}H-NMR(DMSO-d6, δ): 4.31(2H, d, J=5.7 Hz), 4.85(2H, s), 4.91(1H, br t, J=5.7 Hz), 6.45(1H, d, J=7.9 Hz), 7.07(1H, s), 7.13(1H, d, J=7.9 Hz), 7.29–7.36(4H, m), 7.43–7.47(4H, m), .7.60(2H, d, J=8.1 Hz), 7.65(2H, d, J=7.6 Hz), 7.73–7.76 (2H, m).

IR(Nujol): 1574 cm^{-1}.

PRODUCTION EXAMPLE 23

Production of N-(2-pyridylmethyl)-4-acetylamino-3-nitrobenzamide

Oxalyl chloride (1.25 g) was added dropwise to a solution of 1.00 g of 4-acetylamino-3-nitrobenzoic acid and 0.20 g of N,N-dimethylformamide in 15 ml of methylene chloride while being cooled with ice. The mixture was further stirred at room temperature for 1 hour. The reaction solution was concentrated, and diisopropyl ether was added thereto for crystallization. The crystals were added to a solution of 0.483 g of 2-aminomethylpyridine and 0.35 g of triethylamine in 15 ml of methylene chloride. After the mixture was stirred at room temperature for 1 hour, the organic layer was washed twice with water (100 ml×2) and then with 100 ml of a sodium hydrogencarbonate aqueous solution. The organic layer was concentrated to give 0.99 g of N-(2-pyridylmethyl)-4-acetylamino-3-nitrobenzamide.

Properties of the compound:

^{1}H-NMR($CDCl_3$, δ): 2.33(3H, s), 4.76(2H, d, J=4.8 Hz), 7.25(1H, dd, J=5.0 and 7.2 Hz), 7.34(1H, d, J=7.9 Hz), 7.71(1H, dt, J=1.8 and 7.8 Hz), 7.84(1H, s), 8.14(1H, dd, J=2.1 and 8.8 Hz), 8.58(1H, d, J=4.9 Hz), 8.77(1H, d, J=2.1 Hz), 8.90(1H, d, J=8.0 Hz), 10.47(1H, s).

PRODUCTION EXAMPLE 24

Production of N-(2-pyridylmethyl)-4-acetylamino-3-aminobenzamide

Five-percent palladium on carbon (2.53 g) was added to a solution of 10.0 g of N-(2-pyridylmethyl)-4-acetylamino-

3-nitrobenzamide in 150 ml of methanol, and the mixture was stirred in a hydrogen atmosphere at 60° C. for 15 hours. The solid material was separated through filtration, and the filtrate was concentrated. The resulting residue was purified through silica-gel column chromatography (eluent: a mixture of ethyl acetate and methanol at a ratio of 7:3) to give 8.02 g of N-(2-pyridylmethyl)-4-acetylamino-3-aminobenzamide.

Properties of the compound:

^{1}H-NMR(DMSO-d6, δ): 2.06(3H, s), 4.52(2H, d, J=5.9 Hz), 5.09(2H, s), 7.10(1H, dd, J=1.9 and 8.2 Hz), 7.22–7.30 (3H, m), 7.38(1H, d, J=8.2 Hz), 7.75(1H, dt, J=1.7 and 7.6 Hz), 8.50(1H, d, J=4.6 Hz), 8.84(1H, t, J=5.8 Hz), 9.19(1H, s).

PRODUCTION EXAMPLE 25

Production of N-(2-pyridylmethyl)-4-acetylamino-3-(4-benzyloxybenzylamino)benzamide

A solution of 0.80 g of N-(2-pyridylmethyl)-4-acetylamino-3-aminobenzamide in 10 ml of N,N-dimethylformamide were added 1.31 g of 4-benzyloxybenzyl chloride and 1.18 g of sodium hydrogencarbonate, and the mixture was stirred at 90° C. for 2 hours. Chloroform and water were added to the reaction solution, and the chloroform extraction was conducted. The organic layer was washed with water, concentrated, and purified through silica-gel column chromatography to give 0.434 g of N-(2-pyridylmethyl)-4-acetylamino-3-(4-benzyloxybenzylamino)benzamide.

Properties of the compound:

^{1}H-NMR(DMSO-d6, δ): 2.07(3H, s), 4.30(2H, d, J=5.6 Hz), 4.51(2H, d, J=5.9 Hz), 5.07(2H, s), 5.68(1H, t, J=5.6 Hz), 6.97(2H, d, J=8.6 Hz), 7.14(2H, m), 7.25(2H, dd, J=3.4 and 7.4 Hz), 7.32(4H, t, 7.5 Hz), 7.38(2H, t, J=7.1 Hz), 7.44(2H, d, J=7.2 Hz), 7.72(1H, dt, J=1.8 and 7.7 Hz), 8.49(1H, dd, J=1.9 and 5.3 Hz), 8.89(1H, t, J=5.9 Hz), 9.28(1H, s).

PRODUCTION EXAMPLE 26

Production of N-(2-pyridylmethyl)-4-acetylamino-3-(3,4-methylenedioxybenzylamino)benzamide

A solution of 0.80 g of N-(2-pyridylmethyl)-4-acetylamino-3-aminobenzamide in 10 ml of N,N-dimethylformamide were added 0.962 g of 3,4-methylenedioxybenzyl chloride and 0.710 g of sodium hydrogencarbonate, and the mixture was stirred at 80° C. for 4 hours. Chloroform and water were added to the reaction solution, and the chloroform extraction was conducted. The organic layer was washed with water, concentrated, and purified through silica-gel column chromatography (eluent: a mixture of ethyl acetate and methanol at a ratio of 9:1) to give 0.49 g of N-(2-pyridylmethyl)-4-acetylamino-3-(3,4-methylenedioxybenzylamino)benzamide.

Properties of the compound:

^{1}H-NMR(DMSO-d6, δ): 2.08(3H, s), 4.29(2H, s), 4.52 (2H, d, J=5.9 Hz), 5.27(1H, s), 5.97(2H, s), 6.84–6.88(2H, m), 6.96(1H, s), 7.10(1H, d, J=1.3 Hz), 7.13(1H, dd, J=1.6 and 8.2 Hz), 7.25–7.32(3H, m), 7.76(1H, dt, J=1.2 and 7.6 Hz), 8.51(1H, d, J=4.8 Hz), 8.90(1H, t, J=5.8 Hz), 9.28(1H, s).

PRODUCTION EXAMPLE 27

Production of N-(2-pyridylmethyl)-4-acetylamino-3-[4-(1,2,3-thiadiazol-4-yl)benzylamino]benzamide

A solution of 0.800 g of N-(2-pyridylmethyl)-4-acetylamino-3-aminobenzamide in 10 ml of methanol were added 1.08 g of 4-(4-bromomethylphenyl)-1,2,3-thiadiazole and 0.710 g of sodium hydrogencarbonate, and the mixture was stirred at 70° C. for 1 hour. The reaction solution was concentrated, and was purified through silica-gel column chromatography (eluent: a mixture of ethyl acetate and methanol at a ratio of 9:1) to give 0.830 g of N-(2-pyridylmethyl)-4-acetylamino-3-[4-(1,2,3-thiadiazol-4-yl) benzylamino]benzamide

Properties of the compound:

^{1}H-NMR($CDCl_3$, δ): 2.11(3H, s), 4.43–5.56(2H, m), 5.92 (1H, t, J=5.9 Hz), 7.51(1H, d, J=1.4 Hz), 7.15(1H, dd, J=1.6 and 8.1 Hz), 7.22(2H, dd, J=1.9 and 8.1 Hz), 7.33(1H, d, J=8.1 Hz), 7.57(2H, d, J=8.1 Hz), 7.69(1H, dt, J=1.8 and 7.7 Hz), 8.09(2H, d, J=8.2 Hz), 8.47(1H, dd, J=1.9 and 5.2 Hz), 8.89(1H, t, J=5.9 Hz), 9.34(1H, s), 9.58(1H, s).

PRODUCTION EXAMPLE 28

Production of N-benzenesulfonyl-4-acetylamino-3-nitrobenzamide

N,N'-carbonyldiimidazole (14.45 g) was added to a solution of 10.00 g of 4-acetylamino-3-nitrobenzoic acid in 300 ml of N,N-dimethylformamide, and the mixture was stirred at room temperature for 1 hour. Subsequently, 14.03 g of benzenesulfonamide and 13.58 g of diazabicycloundecene were added thereto, and the mixture was stirred at 100° C. for 72 hours. The reaction mixture was separated with the addition of chloroform and water. The organic layer was then concentrated, and the resulting residue was purified through silica-gel column chromatography (eluent: a mixture of ethyl acetate and methanol at a ratio of 4:1) to give 12.67 g of N-benzenesulfonyl-4-acetylamino-3-nitrobenzamide.

Properties of the compound:

^{1}H-NMR(DMSO-d6, δ): 2.08(3H, s), 7.39–7.47(3H, m), 7.65(1H, d, J=8.5 Hz), 7.84(2H, dd, J=1.4 and 7.7 Hz), 8.11(1H, dd, J=1.9 and 8.4 Hz), 8.38(1H, d, J=1.9 Hz), 10.34(1H, s).

PRODUCTION EXAMPLE 29

Production of N-benzenesulfonyl-4-acetylamino-3-aminobenzamide

N-benzenesulfonyl-4-acetylamino-3-nitrobenzamide (12.67 g) was dissolved in 200 ml of methanol and 30 ml of water, and 7.59 g of potassium hydrogencarbonate were further added thereto. The mixture was hydrogenated in a hydrogen atmosphere using 2.53 g of 5% palladium on carbon as catalyst at 40° C. for 24 hours. The solid material was separated through filtration, and the filtrate was concentrated. The resulting residue was purified through silica-gel column chromatography (eluent: a mixture of ethyl acetate and methanol at a ratio of 4:1) to give 6.72 g of N-benzenesulfonyl-4-acetylamino-3-aminobenzamide.

Properties of the compound:

^{1}H-NMR(DMSO-d6, δ): 2.06(3H, s), 7.07(1H, dd, J=1.8 and 8.3 Hz), 7.17(1H, d, J=1.8 Hz), 7.44(1H, d, J=8.3 Hz), 7.61(2H, t), 7.68(1H, t), 7.96(2H, d, J=7.5 Hz), 9.19(1H, s).

IR(Nujol): 1682 cm^{-1}.

PRODUCTION EXAMPLE 30

Production of N-benzenesulfonyl-4-acetylamino-3-(2-nitrobenzylamino)benzamide

In the same manner as in Production Example 32, 0.79 g of N-benzenesulfonyl-4-acetylamino-3-(2-

nitrobenzylamino)benzamide were formed from 0.60 g of N-benzenesulfonyl-4-acetylamino-3-aminobenzamide and 0.52 g of 2-nitrobenzyl bromide.

Properties of the compound:

^{1}H-NMR(DMSO-d6, δ): 2.08(3H, s), 4.72(2H, d, J=5.0 Hz), 5.92(1H, s), 6.86(1H, s), 7.13(1H, d, J=8.1 Hz), 7.31 (1H, d, J=8.0 Hz), 7.49–7.58(3H, m), 7.60(2H, d, J=7.6 Hz), 7.66(1H, t, J=7.4 Hz), 7.86(2H, d, J=7.7 Hz), 8.11(1H, d, J=8.3 Hz), 9.37(1H, s).

PRODUCTION EXAMPLE 31

Production of N-benzenesulfonyl-4-acetylamino-3-benzylaminobenzamide

In the same manner as in Production Example 32, 0.38 g of N-benzenesulfonyl-4-acetylamino-3-benzylaminobenzamide were formed from 0.60 g of N-benzenesulfonyl-4-acetylamino-3-aminobenzamide and 0.47 g of benzyl bromide.

Properties of the compound:

^{1}H-NMR (DMSO-d6, δ): 2.07 (3H, s), 4.35(2H, d, J=5.5 Hz), 5.73(1H, s), 7.06(1H, s), 7.14(1H, d, J=8.3 Hz), 7.21–7.28(2H, m), 7.32(2H, t, J=7.3 Hz), 7.37(2H, d, J=7.6 Hz), 7.53(2H, t, J=7.4 Hz), 7.59(1H, t, J=7.0 Hz), 7.88(2H, d, J=7.7 Hz), 9.29(1H, s), 12.34(1H, s).

PRODUCTION EXAMPLE 32

Production of N-benzenesulfonyl-4-acetylamino-3-(2,4-difluorobenzylamino)benzamide

A solution of 7 ml of methanol containing 0.60 g of N-benzenesulfonyl-4-acetylamino-3-aminobenzamide, 0.656 g of 2,4-difluorobenzyl bromide and 0.423 g of potassium hydrogencarbonate was stirred at 60° C. for 1 hour. The reaction solution was concentrated, and the residue was purified through silica-gel column chromatography (eluent: a mixture of ethyl acetate and methanol at a ratio of 9:1) to give 0.370 g of N-benzenesulfonyl-4-acetylamino-3-(2,4-difluorobenzylamino)benzamide.

Properties of the compound:

^{1}H-NMR(DMSO-d6, δ): 2.05(3H, s), 4.34(2H, d, J=5.5 Hz), 5.60(1H, s), 7.02(1H, t, J=8.0 Hz), 7.06(1H, s), 7.16–7.27(3H, m), 7.38–7.51(4H, m), 7.82(2H, d, J=7.2 Hz), 9.27(1H, s), 12.35(1H, s).

PRODUCTION EXAMPLE 33

Production of N-benzenesulfonyl-4-acetylamino-3-(4-nitrobenzylamino)benzamide

In the same manner as in Production Example 32, 0.52 g of N-benzenesulfonyl-4-acetylamino-3-(4-nitrobenzylamino)benzamide were formed from 0.50 g of N-benzenesulfonyl-4-acetylamino-3-aminobenzamide and 0.436 g of 4-nitrobenzyl bromide.

Properties of the compound:

^{1}H-NMR(DMSO-d6, δ): 2.09(3H, s), 4.54(2H, d, J=5.0 Hz), 6.10(1H, s), 6.89(1H, d, J=1.8 Hz), 7.14(1H, dd, J=1.8 and 8.2 Hz), 7.39(1H, d, J=8.2 Hz), 7.58–7.65(4H, m), 7.68(1H, t, J=7.6 Hz), 7.92(2H, dd, J=1.4 and 7.4 Hz), 8.20(2H, d, J=8.7 Hz), 9.36(1H, s), 12.28(1H, s).

PRODUCTION EXAMPLE 34

Production of N-benzenesulfonyl-4-acetylamino-3-[4-(1,2,3-thiadiazol-4-yl)benzylamino]benzamide

In the same manner as in Production Example 32, 0.38 g of N-benzenesulfonyl-4-acetylamino-3-[4-(1,2,3-thiadiazol-4-yl)benzylamino]benzamide were formed from 0.50 g of N-benzenesulfonyl- 4-acetylamino-3-aminobenzamide and 0.45 g of 4-(4-bromomethylphenyl)-1,2,3-thiadiazole.

Properties of the compound:

^{1}H-NMR(DMSO-d6, δ): 2.10(3H, s), 4.46(2H, d, J=5.3 Hz). 5.96(1H, s), 7.03(1H, s), 7.14(1H, dd, J=1.7 and 8.2 Hz), 7.40(1H, d, J=8.0 Hz), 7.52–7.61(4H, m), 7.65(1H, t, J=7.1 Hz), 7.93(2H, d, J=7.6 Hz), 8.10(2H, d, J=8.2 Hz), 9.35(1H, s), 9.58(1H, s), 12.31(1H, s).

PRODUCTION EXAMPLE 35

Production of ethyl 3-amino-2-nitrobenzoate

A mixture of 20.2 g of 3-acetylamino-2-nitrobenzoic acid, 11.4 g of 97% sulfuric acid and 300 ml of ethanol was stirred for 23 hours while being heat-refluxed. One-hundred milliliters of ethanol were distilled off under reduced pressure, and the residue was cooled to room temperature. Subsequently, the reaction solution was poured into 200 ml of ice water containing 19.5 g of sodium hydrogencarbonate. The crystals precipitated were separated through filtration, and were washed with water. Further, these crystals were dispersed in 30 ml of a mixed solution of ethyl acetate and hexane at a ratio of 1:2. The crystals were separated through filtration, washed with hexane, and then dried to give 18.0 g of ethyl 3-amino-2-nitrobenzoate.

Properties of the compound:

^{1}H-NMR($CDCl_3$, δ): 1.39(3H, t, J=7.1 Hz), 4.37(2H, q, J=7.1 Hz), 6.41(2H, br s), 6.83(1H, d, J=8.7 Hz), 8.00(1H, dd, J=1.8 and 8.7 Hz), 8.85(1H, d, J=1.8 Hz).

PRODUCTION EXAMPLE 36

Production of ethyl 3-acetylamino-2-nitrobenzoate

Acetyl chloride (13 ml) was added dropwise to a solution of 2.98 g of ethyl 3-amino-2-nitrobenzoate and 20 ml of N,N-dimethylaniline in an ice bath. The mixture was stirred at room temperature for 48 hours. The reaction solution was acidified with 10% hydrochloric acid, and was extracted twice with ethyl acetate. The organic layer was washed three times with water. The solvent was distilled off under reduced pressure, and the resulting residue was crystallized with hexane. The crystals were separated through filtration, washed with hexane, and dried to give 3.30 g of ethyl 3-acetylamino-2-nitrobenzoate.

Properties of the compound:

^{1}H-NMR($CDCl_3$, δ): 1.42(3H, t), 2.33(3H, s), 4.42(2H, q), 8.27(1H, dd, J=1.9 and 8.9 Hz), 8.89(1H, d, J=1.9 Hz), 8.91(1H, d, J=8.9 Hz), 10.54(1H, br s).

PRODUCTION EXAMPLE 37

Production of ethyl 4-acetylamino-3-aminobenzoate

A mixture of 149.4 g of ethyl 3-acetylamino-2-nitrobenzoate, 14.9g of 5% palladium on carbon and 1,500 ml of ethanol was stirred in a hydrogen atmosphere for 15 hours. The solid material was separated though filtration, and the filtrate was concentrated. The resulting residue was dissolved in a small amount of ethanol, and diisopropyl ether was added thereto. The crystals precipitated were separated through filtration, and were dried to give 114.4 g of ethyl 4-acetylamino-3-aminobenzoate.

Properties of the compound:

^{1}H-NMR(DMSO-d6, δ): 1.27(3H, t), 2.05(3H, s), 4.23 (2H, q), 5.19(2H, s), 7.13(1H, d, J=8.2 Hz), 7.35(1H, s), 7.47(1H, d, J=8.2 Hz), 9.19(1H, s).

EXAMPLE 24

Synthesis of 1-(2-chlorobenzyl)-6-ethoxycarbonyl-2-methylbenzimidazole (92)

Twenty milliliters of ethanol, 11 ml of acetic acid and 3.07 g of reduced iron were added to 2.07 g of ethyl 3-[N-(2-chlorobenzyl)acetylamino]-4-nitrobenzoate, and the mixture was refluxed for 4 hours. The solid material was separated through filtration, and was washed with ethanol. The filtrate was concentrated, and a sodium hydrogencarbonate aqueous solution was added to the residue. The mixture was extracted with ethyl acetate. The organic layer was dried, and the solvent was then distilled off under reduced pressure. The residue was purified through silica-gel column chromatography (eluent: a mixture of hexane and ethyl acetate at a ratio of from 100/0 to 70:30) to give 1.46 g of 1-(2-chlorobenzyl)-6-ethoxycarbonyl-2-methylbenzimidazole (92).

Properties of Compound (92):

^{1}H-NMR($CDCl_3$, δ): 1.39(3H, t, J=7.1 Hz), 2.57(3H, s), 4.37(2H, q, J=7.1 Hz), 5.46(2H, s), 6.41(1H, d, J=7.8 Hz), 7.10(1H, t, J=7.8 Hz), 7.25(1H, t), 7.47(1H, d, J=8.0 Hz), 7.75(1H, d, J=8.4 Hz), 7.94(1H, s), 8.00(1H, dd, J=1.5 and 8.4 Hz).

EXAMPLE 25

Synthesis of 6-ethoxycarbonyl-1-methyl-2-n-propylbenzimidazole (93)

In the same manner as in Production Example 14, 1.00 g of crude ethyl 3-(N-methylbutyrylamino)-4-nitrobenzoate was obtained from 1.00 g of ethyl 3-butyrylamino-4-nitrobenzoate and 0.843 g of methyl iodide. Subsequently, 0.56 g of 6-ethoxycarbonyl-1-methyl-2-n-propylbenzimidazole (93) were formed in the same manner as in Example 24.

Properties of Compound (93):

^{1}H-NMR($CDCl_3$, δ): 1.08(3H, t, J=7.4 Hz), 1.43(3H, t, J=7.0 Hz), 1.89–1.97(2H, m), 2.89(2H, t, J=7.7 Hz), 3.79 (3H, s), 4.38–4.44(2H, m), 7.71(1H, d, J=8.4 Hz), 7.96(1H, dd, J=8.4 and 1.5 Hz,), 8.05(1H, d, J=1.4 Hz).

EXAMPLE 26

Synthesis of 1-n-butyl-6-ethoxycarbonyl-2-n-propylbenzimidazole (94)

A solution of 1.86 g of ethyl 3-butyrylamino-4-nitrobenzoate in 10 ml of N,N-dimethylformamide was added dropwise to a slurry of 0.428 g of 60% sodium hydride and 10 ml of N,N-dimethylformamide at room temperature, and the mixture was stirred at room temperature for 30 minutes. Subsequently, a solution of 1.97 g of n-butyl iodide in 10 ml of N,N-dimethylformamide was added dropwise thereto, and the mixture was heated at 50° C. for 13 hours. The reaction solution was poured into a mixed solution of 70 g of dilute hydrochloric acid and 70 g of ethyl acetate for extraction. The resulting organic layer was washed twice with water, dried, and then concentrated under reduced pressure to obtain 2.59 g of crude ethyl 3-(N-n-butylbutyrylamino)-4-nitrobenzoate. Then, 0.81 g of 1-n-butyl-6-ethoxycarbonyl-2-n-propylbenzimidazole (94) were formed in the same manner as in Example 24.

Properties of Compound (94):

^{1}H-NMR($CDCl_3$, δ): 0.98(3H, t, J=7.4 Hz), 1.08(3H, t, J=7.4 Hz), 1.43(3H, t, J=7.1 Hz), 1.75–1.83(2H, m), 1.91–1.98(2H, m), 2.88(2H, t, J=7.6 Hz), 4.15(2H, t, J=7.5 Hz), 4.42(2H, q, J=7.2 Hz), 7.73(1H, d, J=8.4 Hz), 7.96(1H, dd, J=8.5 and 1.5 Hz), 8.06(1H, d, J=1.4 Hz).

EXAMPLE 27

Synthesis of 1-(3-chlorobenzyl)-6-ethoxycarbonyl-2-n-propylbenzimidazole (95)

In the same manner as in Production Example 14, crude ethyl 3-[N-(3-chlorobenzyl)butyrylamino]-4-nitrobenzoate was obtained from 1.86 g of ethyl 3-butyrylamino-4-nitrobenzoate and 1.64 g of 3-chlorobenzyl bromide. This compound was converted to 1-(3-chlorobenzyl)-6-ethoxycarbonyl-2-n-propylbenzimidazole [(95), 0.57 g] in the same manner as in Example 24 without being purified.

Properties of Compound (95):

^{1}H-NMR($CDCl_3$, δ): 1.02(3H, t, J=7.4 Hz), 1.39(3H, t, J=7.1 Hz), 1.85–1.92(2H, m), 2.80(2H, t, J=7.5 Hz), 4.38 (2H, q, J=7.1 Hz), 5.37(2H, s), 6.86(1H, d, J=7.4 Hz), 7.04(1H, s), 7.21–7.29(2H, m), 7.77(1H, d, J=8.4 Hz), 7.96(1H, d, J=1.2 Hz), 7.99(1H, dd, J=8.5 and 1.5 Hz).

EXAMPLE 28

Synthesis of 1-benzyl-6-ethoxycarbonyl-2-n-propylbenzimidazole (96)

In the same manner as in Production Example 14, ethyl 3-(N-benzylbutyrylamino]-4-nitrobenzoate was obtained from 1.86 g of ethyl 3-butyrylamino-4-nitrobenzoate and 1.36 g of benzyl bromide. This compound was converted to 1-benzyl-6-ethoxycarbonyl-2-n-propylbenzimidazole [(96), 0.97 g] in the same manner as in Example 24 without being purified.

Properties of Compound (96):

^{1}H-NMR($CDCl_3$, δ): 1.01(3H, t, J=7.4 Hz), 1.39(3H, t, J=7.1 Hz), 1.83–1.91(2H, m), 2.81(2H, t, J=7.5 Hz), 4.37 (2H, q, J=7.1 Hz), 5.40(2H, s), 7.03(1H, d, J=6.4 Hz), 7.28–7.33(3H, m), 7.76(1H, d, J=8.4 Hz), 7.98(1H, dd, J=8.4 and 1.2 Hz), 8.00(1H, s).

EXAMPLE 29

Synthesis of 1-(4-chlorobenzyl)-6-ethoxycarbonyl-2-n-propylbenzimidazole (97)

In the same manner as in Production Example 14, ethyl 3-[N-(4-chlorobenzyl)butyrylamino]-4-nitrobenzoate was obtained from 1.86 g of ethyl 3-butyrylamino-4-nitrobenzoate and 1.64 g of 4-chlorobenzyl bromide. This compound was converted to 1-(4-chlorobenzyl)-6-ethoxycarbonyl-2-n-propylbenzimidazole [(97), 1.06 g] in the same manner as in Example 24 without being purified.

Properties of Compound (97):

^{1}H-NMR($CDCl_3$, δ): 1.02(3H, t, J=7.4 Hz), 1.39(3H, t, J=7.1 Hz), 1.83–1.92(2H, m), 2.80(2H, t, J=7.8 Hz), 4.38 (2H, q, J=7.5 Hz), 5.36(2H, s), 6.96(2H, d, J=8.2 Hz), 7.29(2H, d, J=8.3 Hz), 7.76(1H, d, J=8.4 Hz), 7.96(1H, d, J=1.2 Hz), 7.99(1H, dd, J=8.3 and 1.2 Hz).

EXAMPLE 30

Synthesis of 6-ethoxycarbonyl-2-methyl-1-[2-(trifluoromethyl)benzyl]benzimidazole (98)

In the same manner as in Example 24, 1.32 g of 6-ethoxycarbonyl-2-methyl-1-[2-(trifluoromethyl)benzyl] benzimidazole (98) were formed from 1.82 g of ethyl 4-nitro-3-[N-[2-(trifluoromethyl)benzyl]acetylamino] benzoate.

Properties of Compound (98):

^{1}H-NMR($CDCl_3$, δ): 1.38(3H, t, J=7.1 Hz), 2.53(3H, s), 4.37(2H, q, J=7.1 Hz), 5.58(2H, s), 6.47(1H, d, J=7.7 Hz), 7.36(1H, t, J=7.5 Hz), 7.41(1H, t, J=7.5 Hz), 7.75–7.97(2H, m), 7.94(1H, d, J=1.0 Hz), 8.02(1H, dd, J=1.6 and 8.6 Hz).

EXAMPLE 31

Synthesis of 6-ethoxycarbonyl-2-methyl-1-[4-(trifluoromethyl)benzyl]benzimidazole (99)

In the same manner as in Example 24, 1.22 g of 6-ethoxycarbonyl-2-methyl-1-[4-(trifluoromethyl)benzyl] benzimidazole (99) were formed from 1.52 g of ethyl 4-nitro-3-[N-[4-(trifluoromethyl)benzyl]acetylamino] benzoate.

Properties of Compound (99):

^{1}H-NMR($CDCl_3$, δ): 1.39(3H, t, J=7.1 Hz), 2.58(3H, s), 4.38(2H, q, J=7.1 Hz), 5.44(2H, s), 7.15(2H, d, J=8.2 Hz), 7.59(2H, d, J=8.2 Hz), 7.75(1H, d, J=8.3 Hz), 7.97(1H, s), 8.00(1H, dd, J=1.5 and 8.5 Hz).

EXAMPLE 32

Synthesis of 1-(3,4-dichlorobenzyl)-6-ethoxycarbonyl-2-methylbenzimidazole (100)

In the same manner as in Production Example 14, ethyl 3-[N-(3,4-dichlorobenzyl)acetylamino]-4-nitrobenzoate was obtained from 1.50 g of ethyl 3-acetylamino-4-nitrobenzoate and 1.74 g of 3,4-dichlorobenzyl bromide. This compound was converted to 1-(3,4-dichlorobenzyl)-6-ethoxycarbonyl-2-methylbenzimidazole [(100), 0.76 g] in the same manner as in Example 24 without being purified.

Properties of Compound (100):

^{1}H-NMR($CDCl_3$, δ): 1.40(3H, t, J=7.1 Hz), 2.58(3H, s), 4.39(2H, q, J=7.2 Hz), 5.33(2H, s), 6.84(1H, dd, J=8.4 and 2.3 Hz), 7.16(2H, d, J=2.0 Hz), 7.39(1H, d, J=8.3 Hz), 7.74(1H, d, J=8.4 Hz), 7.96(1H, d, J=1.2 Hz), 8.00(1H, dd, J=8.4 and 1.5 Hz).

EXAMPLE 33

Synthesis of 1-(biphenyl-4-ylmethyl)-6-ethoxycarbonyl-2-methylbenzimidazole (101)

In the same manner as in Production Example 14, 1.44 g of crude ethyl 3-[N-biphenyl-4-ylmethyl)acetylamino]-4-nitrobenzoate were obtained from 1.51 g of ethyl 3-acetylamino-4-nitrobenzoate and 1.46 g of 4-chloromethylbiphenyl. Subsequently, 1.13 g of 1-(biphenyl-4-ylmethyl)-6-ethoxycarbonyl-2-methylbenzimidazole (101) were formed in the same manner as in Example 24.

Properties of Compound (101):

^{1}H-NMR($CDCl_3$, δ): 1.39(3H, t, J=7.1 Hz), 2.62(3H, s), 4.38(2H, q, J=7.1 Hz), 5.42(2H, s), 7.11(2H, d, J=8.2 Hz), 7.34(1H, m), 7.42(2H, m), 7.54(4H, m), 7.74(1H, d, J=8.4 Hz), 7.99(1H, dd, J=1.5 and 8.4 Hz), 8.06(1H, d, J=1.5 Hz).

EXAMPLE 34

Synthesis of 6-ethoxycarbonyl-2-methyl-1-(2-methylbenzyl)benzimidazole (102)

In the same manner as in Production Example 14, ethyl 3-[N-(2-methylbenzyl)acetylamino]-4-nitrobenzoate was obtained from 1.50 g of ethyl 3-acetylamino-4-nitrobenzoate and 1.65 g of 2-methylbenzyl bromide. This compound was converted to 6-ethoxycarbonyl-2-methyl-1-(2-methylbenzyl)benzimidazole [(102), 0.81 g] in the same manner as in Example 24 without being purified.

Properties of Compound (102):

^{1}H-NMR($CDCl_3$, δ): 1.38(3H, t, J=7.2 Hz), 2.43(3H, s), 2.54(3H, s), 4.36(2H, q, J=7.2 Hz), 5.33(2H, s), 6.35(1H, d, J=7.7 Hz), 7.03(1H, t, J=8.2 Hz), 7.18–7.25(2H, m), 7.75 (1H, d, J=8.5 Hz), 7.91(1H, d, J=1.2 Hz), 7.98(1H, dd, J=8.5 and 1.5 Hz).

EXAMPLE 35

Synthesis of 6-ethoxycarbonyl-1-(2-methoxybenzyl)-2-methylbenzimidazole (103)

In the same manner as in Production example 14, crude ethyl 3-[N-(2-methoxybenzyl)acetylamino]-4-nitrobenzoate was obtained from 1.16 g of ethyl 3-acetylamino-4-nitrobenzoate and 1.44 g of 2-methoxybenzyl chloride. Subsequently, 1.18 g of 6-ethoxycarbonyl-1-(2-methoxybenzyl)-2-methylbenzimidazole (103) were formed in the same manner as in Example 24.

Properties of Compound (103):

^{1}H-NMR($CDCl_3$, δ): 1.39(3H, t, J=7.2 Hz), 2.60(3H, s), 3.90(3H, s), 4.37(2H, q, J=7.2 Hz), 5.36(2H, s), 6.61(1H, d, J=7.4 Hz), 6.82(1H, t, J=7.5 Hz), 6.92(1H, d, J=8.3 Hz), 7.27(1H, m), 7.71(1H, d, J=8.4 Hz), 7.96(1H, dd, J=1.5 and 8.4 Hz), 8.03(1H, d, J=1.3 Hz).

EXAMPLE 36

Synthesis of 6-ethoxycarbonyl-1-(4-methoxybenzyl)-2-methylbenzimidazole (104)

In the same manner as in Production Example 14, crude ethyl 3-[N-(4-methoxybenzyl)acetylamino]-4-nitrobenzoate was obtained from 1.60 g of ethyl 3-acetylamino-4-nitrobenzoate and 1.49 g of 4-methoxybenzyl chloride. Subsequently, 1.27 g of 6-ethoxycarbonyl-1-(4-methoxybenzyl)-2-methylbenzimidazole (104) were formed in the same manner as in Example 24.

Properties of Compound (104):

^{1}H-NMR($CDCl_3$,δ): 1.40(3H, t, J=7.1 Hz), 2.59(3H, s), 3.77(3H, s), 4.38(2H, q, J=7.1 Hz), 5.31(2H, s), 6.84(2H, m), 7.00(2H, m), 7.71(1H, d, J=8.4 Hz), 7.97(1H, dd, J=1.4 and 8.4 Hz), 8.03(1H, d, J=1.3 Hz).

EXAMPLE 37

Synthesis of 1-[2-(benzenesulfonylmethyl)benzyl]-6-ethoxycarbonyl-2-methylbenzimidazole (105)

In the same manner as in Production Example 14, ethyl 3-[N-[2-(benzenesulfonylmethyl)benzyl]acetylamino]-4-nitrobenzoate was obtained from 1.00 g of ethyl 3-acetylamino-4-nitrobenzoate and 1.93 g of 2-(benzenesulfonylmethyl)benzyl bromide. This compound was converted to 1-[2-benzenesulfonylmethyl)benzyl]-6-ethoxycarbonyl-2-methylbenzimidazole [(105), 0.89 g] in the same manner as in Example 24 without being purified.

Properties of Compound (105):

^{1}H-NMR($CDCl_3$, δ): 1.37(3H, t, J=7.1 Hz), 2.57(3H, s), 4.36(2H, q, J=7.1 Hz), 4.50(2H, s), 5.60(2H, s), 6.38(1H, d, J=6.7 Hz), 6.88(1H, dd, J=1.5 and 7.3 Hz), 7.10–7.18(2H, m), 7.57(2H, t, J=7.6 Hz), 7.69–7.78(2H, m), 7.79(1H, dd, J=0.8 and 8.1 Hz), 7.92(1H, d, J=1.2 Hz), 7.99(1H, dd, J=1.5 and 8.4 Hz).

EXAMPLE 38

Synthesis of 1-(2-cyanobenzyl)-6-(2-cyanobenzyloxycarbonyl)-2-methylbenzimidazole (106)

In the same manner as in Example 24, 1.75 g of 1-(2-cyanobenzyl)-6-(2-cyanobenzyloxycarbonyl)-2-methylbenzimidazole (106) were formed from 3.33 g of 2-cyanobenzyl 3-[N-(2 -cyanobenzyl)acetylamino]-4-nitrobenzoate.

Properties of Compound (106):

^{1}H-NMR($CDCl_3$, δ): 2.60(3H, s), 5.55(2H, s), 5.60(2H, s), 6.68(1H, d, J=7.3 Hz), 7.41–7.48(3H, m), 7.61(2H, m), 7.72(1H, d, J=7.6 Hz), 7.76(1H, d, J=7.6 Hz), 7.77(1H, d, J=8.6 Hz), 8.02(1H, s), 8.05(1H, dd, J=8.4 and 1.5 Hz).

EXAMPLE 39

Synthesis of 1-(biphenyl-2-ylmethyl)-6-ethoxycarbonyl-2-methylbenzimidazole (107)

In the same manner as in Production Example 14, ethyl 3-[N-(biphenyl-2-ylmethyl)acetylamino]-4-nitrobenzoate was obtained from 1.00 g of ethyl 3-acetylamino-4-nitrobenzoate and 1.47 g of 2-bromomethylbiphenyl. This compound was converted to 1-(biphenyl-2-ylmethyl)-6-ethoxycarbonyl-2-methylbenzimidazole [(107), 1.31 g] in the same manner as in Example 24 without being purified.

Properties of Compound (107):

^{1}H-NMR($CDCl_3$, δ): 1.41(3H, t, J=7.3 Hz), 2.39(3H, s), 4.38(2H, q, J=7.3 Hz), 5.27(2H, s), 6.68(1H, d, J=7.9 Hz), 7.21(1H, dt, J=9.0 and 2.1 Hz), 7.32–7.39(4H, m), 7.43(1H, dd, J=7.3 and 1.9 Hz), 7.46–7.51(2H, m), 7.68(1H, d, J=8.4 Hz), 7.87(1H, d, J=1.3 Hz), 7.95(1H, dd, J=8.4 and 1.5H).

EXAMPLE 40

Synthesis of 1-benzyl-6-ethoxycarbonyl-2-methylbenzimidazole (108)

In the same manner as in Production Example 14, ethyl 3-(N-benzylacetylamino)-4-nitrobenzoate was obtained from 1.00 g of ethyl 3-acetylamino-4-nitrobenzoate and 1.02 g of benzyl bromide. This compound was converted to 1-benzyl-6-ethoxycarbonyl-2-methylbenzimidazole [(108), 0.71 g] in the same manner as in Example 24 without being purified.

Properties of Compound (108):

^{1}H-NMR($CDCl_3$, δ): 1.39(3H, t, J=7.1 Hz), 2.58(3H, s), 4.38(2H, q, J=7.1 Hz), 5.38(2H, s), 7.05(2H, dd, J=8.3 and 1.8 Hz), 7.28–7.33(3H, m), 7.72(1H, d, J=8.4 Hz), 7.98(1H, dd, J=8.4 and 1.5 Hz), 8.02(1H, d, J=1.2 Hz).

EXAMPLE 41

Synthesis of 1-(4-tert-butylbenzyl)-6-ethoxycarbonyl-2-methylbenzimidazole (109)

In the same manner as in Production Example 14, ethyl 3-[N-(4-tert-butylbenzyl)acetylamino]-4-nitrobenzoate was obtained from 1.00 g of ethyl 3-acetylamino-4-nitrobenzoate and 1.35 g of 4-tert-butylbenzyl bromide. This compound was converted to crude 1-(4-tert-butylbenzyl)-6-ethoxycarbonyl-2-methylbenzimidazole [(109), 1.60 g] in the same manner as in Example 24 without being purified.

EXAMPLE 42

Synthesis of 6-ethoxycarbonyl-2-methyl-1-(2-naphthylmethyl)benzimidazole (110)

In the same manner as in Production example 14, ethyl 3-[N-(2-naphthylmethyl)acetylamino]-4-nitrobenzoate was obtained from 1.00 g of ethyl 3-acetylamino-4-nitrobenzoate and 1.32 g of 2-naphthylmethyl bromide. This compound was converted to crude 6-ethoxycarbonyl-2-methyl-1-(2-naphthylmethyl)benzimidazole [(110), 1.28 g] in the same manner as in Example 24 without being purified.

EXAMPLE 43

Synthesis of 1-(biphenyl-4-ylmethyl)-6-ethoxycarbonyl-2-ethylbenzimidazole (111)

In the same manner as in Production Example 14, ethyl 3-[N-(biphenyl-4-ylmethyl)propionylamino]-4-nitrobenzoate was obtained from 2.00 g of ethyl 4-nitro-3-propionylaminobenzoate and 2.28 g of 4-chloromethylbiphenyl. This compound was converted to 1-(biphenyl-4-ylmethyl)-6-ethoxycarbonyl-2-ethylbenzimidazole [(111), 2.07 g)] in the same manner as in Example 24 without being purified.

Properties of Compound (111):

^{1}H-NMR($CDCl_3$, δ): 1.39(3H, t, J=7.2 Hz), 1.45(3H, t, J=7.5 Hz), 2.90(2H, q, J=7.5 Hz), 4.38(2H, q, J=7.2 Hz), 5.43(2H, s), 7.10(2H, d, J=8.3 Hz), 7.33–7.36(1H, m), 7.43(2H, t, J=7.4 Hz), 7.51– 7.56(4H, m), 7.79(1H, d, J=8.5 Hz), 7.80(1H, dd, J=1.5 and 8.4 Hz), 8.05(1H, d, J=1.3 Hz).

EXAMPLE 44

Synthesis of 1-(2-chlorobenzyl)-5-ethoxycarbonyl-2-methylbenzimidazole (112)

In the same manner as in Production Example 14, ethyl 4-[N-(2-chlorobenzyl)acetylamino]-3-nitrobenzoate was obtained from 3.15 g of ethyl 4-acetylamino-3-nitrobenzoate and 3.85 g of 2-chlorobenzyl bromide. This compound was converted to 1-(2-chlorobenzyl)-5-ethoxycarbonyl-2-methylbenzimidazole [(112), 2.54 g] in the same manner as in Example 24 without being purified.

Properties of Compound (112):

^{1}H-NMR($CDCl_3$, δ): 1.41(3H, t, J=7.1 Hz), 2.59(3H, s), 4.40(2H, q, J=7.1 Hz), 5.43(1H, s), 6.43(1H, d, J=7.8 Hz), 7.10(1H, t, J=7.5 Hz), 7.19(1H, d, J=8.5 Hz), 7.25(1H, m), 7.46(1H, d, J=8.1 Hz), 7.95(1H, dd, J=1.4 and 8.4 Hz), 8.47(1H, s).

EXAMPLE 45

Synthesis of 1-(2,6-dichlorobenzyl)-6-ethoxycarbonyl-2-methylbenzimidazole (113)

In the same manner as in Production Example 14, ethyl 3-[N-(2,6-dichlorobenzyl)acetylamino]-4-nitrobenzoate was obtained from 1.50 g of ethyl 3-acetylamino-4-nitrobenzoate and 2.14 g of 2,6-dichlorobenzyl bromide. This compound was converted to 1-(2,6-dichlorobenzyl)-6-ethoxycarbonyl-2-methylbenzimidazole [(113), 0.91 g] in the same manner as in Example 24 without being purified.

Properties of Compound (113):

^{1}H-NMR($CDCl_3$, δ): 1.38(3H, t, J=7.1 Hz), 2.64(3H, s), 4.34(2H, q, J=7.1 Hz), 5.61(2H, s), 7.30(1H, dd, J=7.6 and 8.5 Hz), 7.40(2H, d, J=8.0 Hz), 7.66(1H, d, J=8.4 Hz), 7.87(1H, d, J=1.1 Hz), 7.91(1H, dd, J=8.4 and 1.5 Hz).

EXAMPLE 46

Synthesis of 6-ethoxycarbonyl-2-n-propyl-1-i-propylbenzimidazole (114)

Two milliliters of acetic acid were added to 0.06 g of ethyl 4-amino-3-(N-i-propylbutyrylamino)benzoate, and the mix-

ture was stirred at 90° C. for 14 hours. The reaction solution was concentrated under reduced pressure to give 0.05 g of 6-ethoxycarbonyl-2-n-propyl-1-i-propylbenzimidazole (114).

Properties of Compound (114):

^{1}H-NMR($CDCl_3$, δ): 1.07(3H, t, J=7.4 Hz), 1.43(3H, t, J=7.0 Hz), 1.69(6H, d, J=6.9 Hz), 1.85–1.92(2H, m), 2.91 (2H, t, J=7.7 Hz), 4.41(2H, q, J=7.3 Hz), 4.67–4.76(1H, m), 7.72(1H, d, J=8.3 Hz), 7.94(1H, dd, J=8.7 and 1.5 Hz), 8.25(1H, d, J=1.2 Hz).

EXAMPLE 47

Synthesis of 2-benzyl-6-ethoxycarbonyl-1-methylbenzimidazole (115)

A solution of 0.924 g of ethyl 4-nitro-3-phenylacetylaminobenzoate in 10 ml of N,N-dimethylformamide were added 0.166 g of 60% sodium hydride while being cooled with ice, and the mixture was stirred at room temperature for 1 hour. Methyl iodide (0.50 ml) was added thereto, and the resulting mixture was stirred at room temperature for 1 hour. The reaction solution was poured into cold 1–N hydrochloric acid, and the mixture was extracted twice with ethyl acetate. The organic layer was washed with 1–N hydrochloric acid and then with water, and was dried. The solvent was distilled off under reduced pressure. The residue was purified through silica-gel column chromatography (developing eluent: a mixture of ethyl acetate and hexane at a ratio of from 1:10 to 1:4) to obtain 0.510 g of ethyl 4-nitro-3-[N-(methyl)phenylacetylamino] benzoate. To 0.148 g of this compound were added 2 ml of ethanol, 1 ml of acetic acid and 0.240 g of reduced iron, and the mixture was refluxed for 2 hours. The solid material was separated through filtration. The filtrate was concentrated, and was then purified through preparative thin-layer silica-gel chromatography (eluent: a mixture of chloroform and ethyl acetate at a ratio of 2:1) to give 0.090 g of 2-benzyl-6-ethoxycarbonyl-1-methylbenzimidazole (115).

Properties of Compound (115):

^{1}H-NMR($CDCl_3$, δ): 1.41(3H, t, J=7.1 Hz), 3.63(3H, s), 4.32(2H, s), 4.40(2H, q, J=7.1 Hz), 7.21–7.26(3H, m), 7.27–7.32(2H, m), 7.72(1H, d, J=8.4 Hz), 7.98(1H, dd, J=1.5 and 8.4 Hz), 8.03(1H, d, J=1.3 Hz).

EXAMPLE 48

Synthesis of 1-(2,4-dichlorobenzyl)-6-ethoxycarbonyl-2-methylbenzimidazole (116)

A solution of 1.50 g of ethyl 3-acetylamido-4-nitrobenzoate in 8 ml of N,N-dimethylformamide was added dropwise to a slurry of 0.357 g of 60% sodium hydride and 8 ml of N,N-dimethylformamide at room temperature, and the mixture was stirred for 30 minutes. Subsequently, a solution of 1.74 g of 2,4-dichlorobenzyl chloride in 8 ml of N,N-dimethylformamide was added dropwise thereto, and the mixture was stirred for 30 minutes. The reaction solution was poured into a mixed solution of 50 g of dilute hydrochloric acid and 60 g of ethyl acetate for separation. The resulting organic layer was washed twice with 50 g of water. This organic layer was concentrated under reduced pressure to obtain 3.5 g of crude ethyl 3-[N-(2,4-dichlorobenzyl) acetylamino]-4-nitrobenzoate. This compound without being purified was dissolved in 23 ml of ethanol and 12 ml of acetic acid, and then 3.32 g of reduced iron were added thereto. The mixture was heat-refluxed for 6 hours. The solid material was removed using a filtration aid, and the filtrate was concentrated under reduced pressure. The resulting residue was separated with the addition of 60 ml of ethyl acetate and 50 ml of dilute hydrochloric acid. The organic layer was washed with 50 g of a saturated aqueous solution of sodium hydrogencarbonate and then twice with 50 g of water, and was concentrated under reduced pressure. The resulting residue was purified through silica-gel column chromatography (eluent: a mixture of hexane and ethyl acetate at a ratio of from 4:1 to 1:1) to give 0.94 g of 1-(2,4-dichlorobenzyl)-6-ethoxycarbonyl-2-methylbenzimidazole (116).

Properties of Compound (116):

^{1}H-NMR($CDCl_3$, δ): 1.40(3H, t, J=7.1 Hz), 2.56(3H, s), 4.38(2H, q, J=7.1 Hz), 5.41(2H, s), 6.34(1H, d, J=8.4 Hz), 7.09(1H, dd, J=8.4 and 2.0 Hz), 7.49(1H, d, J=2.0 Hz), 7.75(1H, d, J=8.4 Hz), 7.92(1H, s), 8.00(1H, dd, J=8.5 and 1.4 Hz).

EXAMPLE 49

Synthesis of 6-carboxy-1-(4-chlorobenzyl)-2-n-propylbenzimidazole (117)

1.06 g of 1-(4-chlorobenzyl)-6-ethoxycarbonyl-2-n-propylbenzimidazole were added 3.57 g of a 10% sodium hydroxide aqueous solution, 5 ml of ethanol and 3.57 g of water, and the mixture was heat-refluxed for 1 hour. The reaction solution was adjusted to a pH of 6 with 10% hydrochloric acid, and was concentrated under reduced pressure. Ethanol was added to the resulting residue, and the inorganic salt was separated through filtration. The filtrate was concentrated under reduced pressure to obtain 0.80 g of the residue. This residue was purified through silica-gel column chromatography (eluent: a mixture of ethyl acetate and methanol at a ratio of 4:1) to give 0.63 g of 6-carboxy-1-(4-chlorobenzyl)-2-n-propylbenzimidazole (117).

Properties of Compound (117)

^{1}H-NMR(DMSO-d6, δ): 0.96(3H, t, J=7.3 Hz), 1.76–1.88 (2H, m), 3.10–3.23(2H, m), 5.83(2H, s), 7.27(2H, d, J=8.4 Hz), 7.44(2H, d, J=8.4 Hz), 7.89(1H, d, J=8.4 Hz), 7.89(1H, d, J=8.5 Hz), 8.28(1H, s).

EXAMPLE 50

Synthesis of 6-carboxy-1-methyl-2-n-propylbenzimidazole (118)

In the same manner as in Example 49, 0.46 g of 6-carboxy-1-methyl-2-n-propylbenzimidazole (118) were formed from 0.56 g of 6-ethoxycarbonyl-1-methyl-2-n-propylcarbonylbenzimidazole.

Properties of Compound (118):

^{1}H-NMR(DMSO-d6, δ): 1.00(3H, t, J=7.3 Hz), 1.79–1.93 (2H, m), 3.06(3H, t, J=7.4 Hz), 3.92(3H, s), 7.76(1H, d, J=8.4 Hz), 7.97(1H, d, J=8.4 Hz), 8.31(1H, s).

EXAMPLE 51

Synthesis of 6-carboxy-2-n-propyl-1-i-propylbenzimidazole (119)

In the same manner as in Example 49, 0.045 g of 6-carboxy-2-n-propyl-1-i-propylbenzimidazole (119) were formed from 0.045 g of 6-ethoxycarbonyl-2-n-propyl-1-i-propylbenzimidazole.

Properties of Compound (119):

^{1}H-NMR(CD_3OD, δ): 0.98(3H, t, J=7.4 Hz), 1.61(6H, d, J=6.9 Hz), 1.74–1.82(2H, m), 2.89(2H, t, J=7.5 Hz),

3.21–3.24(2H, m), 4.78–4.83(1H, m), 7.51(1H, d, J=8.3 Hz), 7.84(1H, dd, J=8.4 and 1.5 Hz), 8.26(1H, s).

EXAMPLE 52

Synthesis of 1-n-butyl-6-carboxy-2-n-propylbenzimidazole (120)

In the same manner as in Example 49, 0.60 g of 1-n-butyl-6-carboxy-2-n-propylbenzimidazole (120) were formed from 0.81 g of 1-n-butyl-6-ethoxycarbonyl-2-n-propylbenzimidazole.

Properties of Compound (120):

^{1}H-NMR(DMSO-d6, δ): 1.02(3H, t, J=7.3 Hz), 1.17(3H, t, J=7.3 Hz), 1.33–1.41(2H, m), 1.70–1.77(2H, m), 1.85–1.93(2H, m), 3.07(2H, t, J=7.6 Hz), 4.42(2H, t, J=7.4 Hz), 7.78(1H, d, J=8.5 Hz), 7.99(1H, dd, J=8.5 and 1.0 Hz), 8.35(1H, s), 13.13(1H, s).

EXAMPLE 53

Synthesis of 6-carboxy-1-(2-chlorobenzyl)-2-methylbenzimidazole (121)

Eighty milliliters of ethanol and 37 g of a 10% sodium hydroxide aqueous solution were added to 10.0 g of 1-(2-chlorobenzyl)-6-ethoxycarbonyl-2-methylbenzimidazole, and the mixture was refluxed for 4 hours. The reaction solution was cooled, and was then adjusted to a pH of 6 with 10% hydrochloric acid. The precipitate was collected, washed with water, and dried under reduced pressure to give 8.30 g of 6-carboxy-1-(2-chlorobenzyl)-2-methylbenzimidazole (121).

EXAMPLE 54

Synthesis of 6-carboxy-1-(2,6-dichlorobenzyl)-2-methylbenzimidazole (122)

In the same manner as in Example 53, 0.72 g of 6-carboxy-1-(2,6-dichlorobenzyl)-2-methylbenzimidazole (122) were formed from 0.90 g of 1-(2,6-dichlorobenzyl)-6-ethoxycarbonyl-2-methylbenzimidazole.

Properties of Compound (122):

^{1}H-NMR(DMSO-d6, δ): 2.60(3H, s), 5.71(2H, s), 7.46 (1H, t, J=7.9 Hz), 7.57(3H, t, J=8.2 Hz), 7.73(2H, m), 12.57(1H, s).

EXAMPLE 55

Synthesis of 6-carboxy-2-methyl-1-[2-(trifluoromethyl)benzyl]benzimidazole (123)

In the same manner as in Example 53, 0.98 g of 6-carboxy-2-methyl-1-[2-(trifluoromethyl)benzyl] benzimidazole (123) were formed from 1.17 g of 6-ethoxycarbonyl-2-methyl-1-[2-(trifluoromethyl)benzyl] benzimidazole.

Properties of Compound (123):

^{1}H-NMR(DMSO-d6, δ): 2.49(3H, s), 5.70(2H, s), 6.46–6.51(1H, m), 7.51(2H, m), 7.65(1H, d, J=8.4 Hz), 7.81(1H, dd, J=1.4 and 8.4 Hz), 7.82–7.87(1H, m), 7.91(1H, s).

EXAMPLE 56

Synthesis of 6-carboxy-2-methyl-1-[4-(trifluoromethyl)benzyl]benzimidazole (124)

In the same manner as in Example 53, 1.07 g of 6-carboxy-2-methyl-1-[4-(trifluoromethyl)benzyl]-benzimidazole (124) were formed from 1.22 g of 6-ethoxycarbonyl-2-methyl-1-[4-(trifluoromethyl)benzyl]-benzimidazole.

Properties of Compound (124):

^{1}H-NMR(DMSO-d6, δ): 2.85(3H, s), 5.92(2H, s), 7.50 (2H, d, J=8.1 Hz), 7.74(2H, d, J=8.1 Hz), 7.88(1H, d, J=8.5 Hz), 8.07(1H, d, J=8.5 Hz), 8.31(1H, s), 13.3(1H, br s).

EXAMPLE 57

Synthesis of 6-carboxy-1-(3,4-dichlorobenzyl)-2-methylbenzimidazole (125)

In the same manner as in Example 53, 0.55 g of 6-carboxy-1-(3,4-dichlorobenzyl)-2-methylbenzimidazole (125) were formed from 0.76 g of 1-(3,4-dichlorobenzyl)-6-ethoxycarbonyl-2-methylbenzimidazole.

Properties of Compound (125):

^{1}H-NMR(DMSO-d6, δ): 2.56(3H, s), 5.61(2H, s), 6.98 (1H, dd, J=8.4 and 1.9 Hz), 7.46(1H, d, J=1.9 Hz), 7.59(1H, d, J=8.3 Hz), 7.63(1H, d, J=8.4 Hz), 7.81(1H, dd, J=8.4 and 1.4 Hz), 8.07(1H, s), 12.76(1H, s).

EXAMPLE 58

Synthesis of 1-benzyl-6-carboxy-2-n-propylbenzimidazole (126)

A 10% sodium hydroxide aqueous solution (3.61 g), 5 ml of ethanol and 3 ml of water were added to 0.97 g of 1-benzyl-6-ethoxycarbonyl-2-n-propylbenzimidazole, and the mixture was heat-refluxed for 1 hour. The reaction solution was adjusted to a pH of 6 with 10% hydrochloric acid, and was concentrated under reduced pressure. Ethanol was added to the residue, and the inorganic salt was separated through filtration. The filtrate was concentrated under reduced pressure to give 0.85 g of 1-benzyl-6-carboxy-2-n-propylbenzimidazole (126).

Properties of Compound (126):

^{1}H-NMR(DMSO-d6, δ): 0.94(3H, t, J=7.4 Hz), 1.73–1.81 (2H, m), 2.85(2H, t, J=7.3 Hz), 5.59(2H, s), 7.07(2H, dd, J=1.1 and 8.3 Hz), 7.27(1H, t, J=7.3 Hz), 7.33(2H, t, J=7.4 Hz), 7.65(1H, d, J=8.4 Hz), 7.79(1H, dd, J=1.5 and 8.4 Hz), 8.04(1H, s).

EXAMPLE 59

Synthesis of 6-carboxy-1-(3-chlorobenzyl)-2-n-propylbenzimidazole (127)

In the same manner as in Example 58, 0.35 g of 6-carboxy-1-(3-chlorobenzyl)-2-n-propylbenzimidazole (127) were formed from 0.57 g of 1-(3-chlorobenzyl)-6-ethoxycarbonyl-2-n-propylbenzimidazole.

Properties of Compound (127):

^{1}H-NMR(DMSO-d6, δ): 0.94(3H, t, J=7.3 Hz), 1.70–1.79 (2H, m), 2.83(2H, t, J=7.4 Hz), 5.59(2H, s), 6.94(1H, s), 7.15(1H, s), 7.34(2H, d, J=4.4 Hz), 7.59(1H, d, J=8.4 Hz), 7.81(1H, d, J=8.1 Hz), 8.02(1H, s).

EXAMPLE 60

Synthesis of 6-carboxy-2-methyl-1-(2-nitrobenzyl) benzimidazole (128)

In the same manner as in Example 58, 0.35 g of 6-carboxy-2-methyl-1-(2-nitrobenzyl)benzimidazole (128) were formed from 0.61 g of 6-ethoxycarbonyl-2-methyl-1-(2-nitrobenzyl)benzimidazole.

Properties of Compound (128):

^{1}H-NMR(DMSO-d6, δ): 2.51(3H, s), 5.96(2H, s), 6.33 (1H, d, J=7.0 Hz), 7.55–7.62(2H, m), 7.66(1H, d, J=8.3 Hz), 7.81(1H, d, J=8.4 Hz), 8.06(1H, s), 8.24(1H, d, J=7.0 Hz), 12.66(1H, s).

EXAMPLE 61

Synthesis of 6-carboxy-1-(2-chlorobenzyl)-2-methylbenzimidazole (121)

Ethanol (15 ml) and 10.6 g of a 5% sodium hydroxide aqueous solution were added to 1.456 g of 1-(2-chlorobenzyl)-6-ethoxycarbonyl-2-methylbenzimidazole, and the mixture was refluxed for 1 hour. The reaction solution was cooled, and was then adjusted to a pH of 6 with 10% hydrochloric acid. The precipitate was collected, washed with water, and dried under reduced pressure to give 0.645 g of 6-carboxy-1-(2-chlorobenzyl)-2-methylbenzimidazole (121).

EXAMPLE 62

Synthesis of 6-carboxy-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole (129)

A 10% sodium hydroxide aqueous solution (3.10 g) and 10 ml of ethanol were added to 0.94 g of 1-(2,4-dichlorobenzyl)-6-ethoxycarbonyl-2-methylbenzimidazole, and the mixture was heat-refluxed for 1 hour. The reaction solution was adjusted to a pH of 6 with 10% hydrochloric acid. The crystals precipitated were separated through filtration, and were dried to give 0.68 g of 6-carboxy-1-(2, 4-dichlorobenzyl)-2-methylbenzimidazole (129).

Properties of Compound (129):

^{1}H-NMR(DMSO-d6, δ): 2.52(3H, s), 5.61(2H, s), 6.54 (1H, d, J=8.4 Hz), 7.33(1H, dd, J=8.4 and 2.1 Hz), 7.64(1H, d, J=8.4 Hz), 7.74(1H, d, J=2.1 Hz), 7.81(1H, dd, J=8.4 and 1.5 Hz), 7.98(1H, s), 12.72(1H, s).

EXAMPLE 63

Synthesis of 1-(biphenyl-4-ylmethyl)-6-carboxy-2-methylbenzimidazole (130)

In the same manner as in Example 53, 0.83 g of 1-(biphenyl-4-ylmethyl)-6-carboxy-2-methylbenzimidazole (130) were formed from 1.10 g of 1-(biphenyl-4-ylmethyl)-6-ethoxycarbonyl-2-methylbenzimidazole.

Properties of Compound (130):

^{1}H-NMR(DMSO-d6, δ): 2.53(3H, s), 5.61(2H, s), 7.18 (2H, d, J=8.2 Hz), 7.34(1H, m), 7.43(2H, m), 7.62(5H, m), 7.79(1H, dd, J=1.6 and 8.5 Hz), 8.09(1H, d, J=1.0 Hz), 12.72(1H, br s).

EXAMPLE 64

Synthesis of 1-(4-tert-butylbenzyl)-6-carboxy-2-methylbenzimidazole (131)

In the same manner as in Example 53, 0.55 g of 1-(4-tert-butylbenzyl)-6-carboxy-2-methylbenzimidazole (131) were formed from 1.34 g of 1-(4-tert-butylbenzyl)-6-ethoxycarbonyl-2-methylbenzimidazole.

Properties of Compound (131):

^{1}H-NMR(DMSO-d6, δ): 1.22(9H, s), 2.57(3H, s), 5.52 (2H, s), 7.03(2H, d, J=8.2 Hz), 7.35(1H, d, J=8.3 Hz), 7.60(1H, d, J=8.4 Hz), 7.78(1H, dd, J=8.4 and 1.5 Hz), 8.06(1H, s), 12.71(1H, s).

EXAMPLE 65

Synthesis of 6-carboxy-2-methyl-1-(2-methylbenzyl)benzimidazole (132)

In the same manner as in Example 53, 0.49 g of 6-carboxy-2-methyl-1-(2-methylbenzyl)benzimidazole (132) were formed from 0.81 g of 6-ethoxycarbonyl-2-methyl-1-(2-methylbenzyl)benzimidazole.

Properties of Compound (132):

^{1}H-NMR(DMSO-d6, δ): 2.41(3H, s), 2.48(3H, s), 5.55 (2H, s), 6.14(1H, d, J=7.6 Hz), 7.02(1H, t, J=7.4 Hz), 7.17(1H, t, J=7.3 Hz), 7.26(1H, d, J=7.4 Hz), 7.65(1H, d, J=8.4 Hz), 7.81(1H, dd, J=8.4 and 1.4 Hz), 7.97(1H, d, J=1.1 Hz), 12.71(1H, s).

EXAMPLE 66

Synthesis of 6-carboxy-1-(2-methoxybenzyl)-2-methylbenzimidazole (133)

In the same manner as in Example 53, 1.00 g of 6-carboxy-1-(2-methoxybenzyl)-2-methylbenzimidazole (133) was formed from 1.63 g of 6-ethoxycarbonyl-1-(2-methoxybenzyl)-2-methylbenzimidazole.

Properties of Compound (133):

^{1}H-NMR(DMSO-d6, δ): 2.55(3H, s), 3.81(3H, s), 5.42 (2H, s), 6.77(1H, m), 6.85(1H, m), 7.05(1H, m), 7.28(1H, m), 7.58(1H, m), 7.76(1H, m), 7.99(1H, s), 12.65(1H, br s).

EXAMPLE 67

Synthesis of 6-carboxy-1-(4-methoxybenzyl)-2-methylbenzimidazole (134)

In the same manner as in Example 53, 0.99 g of 6-carboxy-1-(4-methoxybenzyl)-2-methylbenzimidazole (134) were formed from 1.27 g of 6-ethoxycarbonyl-1-(4-methoxybenzyl)-2-methylbenzimidazole.

Properties of Compound (134):

^{1}H-NMR(DMSO-d6, δ): 2.86(3H, s), 3.71(3H, s), 5.69 (2H, s), 6.92(2H, d, J=8.4 Hz), 7.27(2H, d, J=8.4 Hz), 7.84(1H, d, J=8.5 Hz), 8.04(1H, d, J=8.5 Hz), 8.33(1H, s), 13.25(1H, br t).

EXAMPLE 68

Synthesis of 6-carboxy-2-methyl-1-[2-(benzenesulfonylmethyl)benzyl]benzimidazole (135)

In the same manner as in Example 53, 0.74 g of 6-carboxy-2-methyl-1-[2-(benzenesulfonylmethyl)benzyl]-benzimidazole (135) were formed from 0.89 g of 6-ethoxycarbonyl-2-methyl-1-[2-(benzenesulfonylmethyl) benzyl]benzimidazole.

Properties of Compound (135):

^{1}H-NMR(DMSO-d6, δ): 2.44(3H, s), 4.99(2H, s), 5.71 (2H, s), 6.08(1H, d, J=6.5 Hz), 7.12–7.20(3H, m), 7.64–7.70 (3H, m), 7.77–7.83(2H, m), 7.89(2H, s), 7.90(1H, s), 12.71 (1H, s).

EXAMPLE 69

Synthesis of 6-carboxy-1-(2-cyanobenzyl)-2-methylbenzimidazole (136)

In the same manner as in Example 53, 1.14 g of 6-carboxy- 1-(2-cyanobenzyl)-2-methylbenzimidazole (136) were formed from 2.04 g of 1-(2-cyanobenzyl)-6-(2-cyanobenzyloxycarbonyl)-2-methylbenzimidazole.

Properties of Compound (136):

^{1}H-NMR(DMSO-d6, δ): 2.54(3H, s), 5.80(2H, s), 6.78 (1H, d, J=7.8 Hz), 7.51(1H, t, J=7.4 Hz), 7.61(1H, dt, J=7.8 and 1.2 Hz), 7.64(1H, d, J=8.4 Hz), 7.80(1H, dd, J=8.4 and 1.5 Hz), 7.94(1H, d, J=6.7 Hz), 8.00(1H, d, J=1.1 Hz), 12.70(1H, s).

EXAMPLE 70

Synthesis of 6-carboxy-1-(biphenyl-2-ylmethyl)-2-methylbenzimidazole (137)

In the same manner as in Example 53, 1.07 g of 6-carboxy-1-(biphenyl-2-ylmethyl)-2-methylbenzimidazole (137) were formed from 1.31 g of 1-(biphenyl-2-ylmethyl)-6-ethoxycarbonyl-2-methylbenzimidazole.

Properties of Compound (137):

^{1}H-NMR(DMSO-d6, δ): 2.32(3H, s), 5.45(2H, s), 6.61 (1H, d, J=7.7 Hz), 7.26(1H, dt, J=7.7 and 1.4 Hz), 7.31(1H, dd, J=7.5 and 1.3 Hz), 7.36(1H, dt, J=7.5 and 0.7 Hz), 7.40–7.46(1H, m), 7.46–7.52(4H, m), 7.57(1H, d, J=8.4 Hz), 7.76(1H, dd, J=7.9 and 1.5 Hz), 7.86(1H, d, J=1.2 Hz), 12.72(1H, s).

EXAMPLE 71

Synthesis of 1-benzyl-6-carboxy-2-methylbenzimidazole (138)

In the same manner as in Example 53, 0.59 g of 1-benzyl-6-carboxy-2-methylbenzimidazole(138) were formed from 0.71 g of 1-benzyl-6-ethoxycarbonyl-2-methylbenzimidazole.

Properties of Compound (138):

^{1}H-NMR(DMSO-d6, δ): 2.56(3H, s), 5.57(2H, s), 7.11 (1H, d, J=8.0 Hz), 7.27(1H, t, J=7.2 Hz), 7.32–7.35(2H, m), 7.61(1H, d, J=8.3 Hz), 7.79(1H, dd, J=8.4 and 1.3 Hz), 8.06(1H, s), 12.75(1H, s).

EXAMPLE 72

Synthesis of 6-carboxy-2-methyl-1-(2-naphthylmethyl)benzimidazole (139)

In the same manner as in Example 53, 0.80 g of 6-carboxy- 2-methyl-1-(2-naphthylmethyl)benzimidazole (139) were formed from 1.28 g of 6-ethoxycarbonyl-2-methyl-1-(2-naphthylmethyl)benzimidazole.

Properties of Compound (139):

^{1}-NMR(DMSO-d6, δ): 2.61(3H, s), 5.74(2H, s), 7.29(1H, d, J=8.6 Hz), 7.46–7.52(2H, m), 7.59(1H, s), 7.63(1H, d, J=8.3 Hz), 7.78–7.92(4H, m), 8.09(1H, s), 12.68(1H, s).

EXAMPLE 73

Synthesis of 1-(biphenyl-4-ylmethyl)-6-carboxy-2-ethylbenzimidazole (140)

In the same manner as in Example 53, 1.70 g of 1-(biphenyl-4-ylmethyl)-6-carboxy-2-ethylbenzimidazole (140) were formed from 2.07 g of 1-(biphenyl-4-ylmethyl)-6-ethoxycarbonyl-2-ethylbenzimidazole.

Properties of Compound (140):

^{1}H-NMR(DMSO-d6, δ): 1.32(3H, t, J=7.4 Hz), 2.94(2H, q, J=7.5 Hz), 5.63(2H, s), 7.16(2H, d, J=8.2 Hz), 7.34(1H, t, J=7.4 Hz), 7.44(2H, t, J=7.5 Hz), 7.60–7.78(5H, m), 7.81(1H, dd, J=1.4 and 8.4 Hz), 8.10(1H, d, J=1.2 Hz), 12.73(1H, s).

EXAMPLE 74

Synthesis of 5-carboxy-1-(2-chlorobenzyl)-2-methylbenzimidazole (141)

In the same manner as in Example 53, 2.48 g of 5-carboxy-1-(2-chlorobenzyl)-2-methylbenzimidazole (141) were formed from 3.70 g of 1-(2-chlorobenzyl)-5-ethoxycarbonyl-2-methylbenzimidazole.

Properties of Compound (141):

^{1}H-NMR(DMSO-d6, δ): 2.49(3H, s), 5.57(2H, s), 6.53 (1H, d, J=7.8 Hz), 7.22(1H, t, J=7.6 Hz), 7.33(1H, t, J=7.6 Hz), 7.44(1H, d, J=8.4 Hz), 7.54(1H, d, J=8.0 Hz), 7.77(1H, dd, J=1.6 and 8.5 Hz), 8.16(1H, d, J=1.3 Hz), 12.71(1H, br s).

EXAMPLE 75

Synthesis of 5-carboxy-2-methyl-1-(2-nitrobenzyl) benzimidazole (142)

In the same manner as in Example 53, 0.15 g of 5-carboxy- 2-methyl-1-(2-nitrobenzyl)benzimidazole (142) were formed from 0.26 g of 5-ethoxycarbonyl-2-methyl-1-(2-nitrobenzyl)benzimidazole.

Properties of Compound (142):

^{1}H-NMR(DMSO-d6, δ): 2.49(3H, s), 5.91(2H, s), 6.36 (1H, dd, J=7.2 and 1.8 Hz), 7.52(1H, d, J=8.5 Hz), 7.55–7.62 (2H, m), 7.77(1H, dd, J=8.5 and 1.5 Hz), 8.18(1H, d, J=1.3 Hz), 8.24(1H, dd, J=7.4 and 1.6 Hz), 12.69(1H, s).

EXAMPLE 76

Synthesis of 2-benzyl-5-carboxy-1-(2-chlorobenzyl) benzimidazole (143)

In the same manner as in Example 53, 0.488 g of 2-benzyl-5-carboxy-1-(2-chlorobenzyl)benzimidazole (143) were formed from 0.635 g of 2-benzyl-1-(2-chlorobenzyl)-5-ethoxycarbonylbenzimidazole.

Properties of Compound (143):

^{1}H-NMR(DMSO-d6, δ): 4.27(2H, s), 5.57(2H, s), 6.27 (1H, d, J=7.1 Hz), 7.06(1H, t), 7.10–7.29(6H, m), 7.39(1H, d, J=8.6 Hz), 7.47(1H, d, J=7.9 Hz), 7.78(1H, dd, J=1.4 and 8.6 Hz), 8.21(1H, d, J=1.2 Hz), 12.71(1H, br s).

EXAMPLE 77

Synthesis of 2-benzyl-6-carboxy-1-(2-chlorobenzyl) benzimidazole (144)

In the same manner as in Example 53, 0.780 g of 2-benzyl-6-carboxy-1-(2-chlorobenzyl)benzimidazole (144) were formed from 1.00 g of 2-benzyl-1-(2-chlorobenzyl)-6-ethoxycarbonylbenzimidazole.

Properties of Compound (144):

^{1}H-NMR(DMSO-d6, δ): 4.29(2H, s), 5.63(2H, s), 6.28 (1H, d, J=7.8 Hz), 7.07(1H, t, J=7.6 Hz), 7.15(1H, m), 7.19–7.29(5H, m), 7.49(1H, d, J=7.4 Hz), 7.70(1H, d, J=8.4 Hz), 7.81(1H, d, J=8.4 Hz), 7.91(1H, s), 12.73(1H, br s).

EXAMPLE 78

Synthesis of 2-benzyl-5-carboxy-1-(2,4-dichlorobenzyl)benzimidazole (145)

In the same manner as in Example 53, 0.40 g of 2-benzyl-5-carboxy-1-(2,4-dichlorobenzyl)benzimidazole (145) were formed from 0.50 g of 2-benzyl-1-(2,4-dichlorobenzyl)-5-ethoxycarbonylbenzimidazole.

Properties of Compound (145):

^{1}H-NMR(DMSO-d6, δ): 4.28(2H, s), 5.55(2H, s), 6.19 (1H, d, J=8.4 Hz), 7.08–7.22(6H, m), 7.41(1H, d, J=8.4 Hz), 7.62(1H, d, J=2.2 Hz), 7.79(1H, dd, J=1.5 and 8.6 Hz), 8.22(1H, s), 12.72(1H, br s).

EXAMPLE 79

Synthesis of 2-benzyl-6-carboxy-1-(2,4-dichlorobenzyl)benzimidazole (146)

In the same manner as in Example 53, 0.35 g of 2-benzyl-6-carboxy-1-(2,4-dichlorobenzyl)benzimidazole (146) were formed from 0.48 g of 2-benzyl-1-(2,4-dichlorobenzyl)-6-ethoxycarbonylbenzimidazole.

Properties of Compound (146):

^{1}H-NMR(DMSO-d6, δ): 4.30(2H, s), 5.61(2H, s), 6.19 (1H, d, J=8.4 Hz), 7.09–7.22(6H, m), 7.64(1H, d, J=2.1 Hz), 7.71(1H, d, J=8.4 Hz), 7.82(1H, dd, J=1.5 and 8.4 Hz), 7.94(1H, d, J=1.2 Hz), 12.78(1H, br s).

EXAMPLE 80

Synthesis of 1-(biphenyl-4-ylmethyl)-6-carboxy-2-trifluoromethylbenzimidazole (147)

In the same manner as in Example 53, 0.483 g of 1-(biphenyl-4-ylmethyl)-6-carboxy-2-trifluoromethylbenzimidazole (147) were formed from 0.690 g of 1-(biphenyl-4-ylmethyl)-6-ethoxycarbonyl-2-trifluoromethylbenzimidazole.

Properties of Compound (147):

^{1}H-NMR(DMSO-d6, δ): 5.87(2H, s), 7.18(2H, d, J=8.2 Hz), 7.35(1H, t, J=7.4 Hz), 7.44(2H, t, J=7.5 Hz), 7.60–7.67 (4H, m), 7.98(2H, d, J=0.7 Hz), 8.32(1H, s), 13.15(1H, s).

EXAMPLE 81

Synthesis of 1-(biphenyl-4-ylmethyl)-5-carboxy-2-trifluoromethylbenzimidazole (148)

In the same manner as in Example 53, 0.270 g of 1-(biphenyl-4-ylmethyl)-5-carboxy-2-trifluoromethylbenzimidazole (148) were formed from 0.38 g of 1-(biphenyl-4-ylmethyl)-5-ethoxycarbonyl-2-trifluoromethylbenzimidazole.

Properties of Compound (148):

^{1}H-NMR(DMSO-d6, δ): 5.80(2H, s), 7.19(2H, d, J=6.3 Hz), 7.35(1H, t, J=7.2 Hz), 7.43(2H, t, J=7.3 Hz), 7.82(1H, d, J=8.7 Hz), 8.04(1H, d, J=8.7 Hz), 8.45(1H, s).

EXAMPLE 82

Synthesis of 5-ethoxycarbonyl-2-methylbenzimidazole (149)

Reduced iron (6.46 g), 48 ml of ethanol and 24 ml of acetic acid were added to 3.00 g of ethyl 3-acetylamino-4-nitrobenzoate, and the mixture was heat-refluxed for 12 hours. The solid material was removed using a filtration aid, and the filtrate was concentrated under reduced pressure. To the residue were added 100 ml of ethanol and 5.2 g of 35% hydrochloric acid, and the mixture was heat-refluxed for 5 hours. The reaction solution was neutralized with 6.3 g of sodium hydrogencarbonate, and was filtrated. The filtrate was concentrated under reduced pressure. The residue was separated with the addition of 70 ml of ethyl acetate and 70 ml of water. The organic layer was washed three times with water, and the aqueous layer was extracted three times with ethyl acetate. The resulting organic layer was concentrated under reduced pressure to give 1.53 g of a powder of 5-ethoxycarbonyl-2-methylbenzimidazole (149).

Properties of Compound (149):

^{1}H-NMR($CDCl_3$, δ): 1.41(3H, t, J=6.9 Hz), 2.67(3H, s), 4.40(2H, q, J=7.1 Hz), 7.55(1H, d, J=8.4 Hz), 7.96(1H, dd, J=8.4 and 1.5 Hz), 8.27(1H, d, J=1.4 Hz).

EXAMPLE 83

Synthesis of 2-benzyl-5-ethoxycarbonylbenzimidazole (150)

A mixture of 3.60 g of ethyl 3-nitro-4-phenylacetylaminobenzoate, 47 ml of ethanol, 23 ml of acetic acid and 6.4 g of reduced iron was heat-refluxed for 4 hours. The solid material was separated through filtration, and the filtrate was concentrated. To the residue were added 50 ml of ethanol and 5 g of 35% hydrochloric acid. The mixture was stirred for 40 hours while being heat-refluxed. The reaction solution was neutralized with sodium hydrogencarbonate, and was extracted with chloroform. The organic layer was concentrated under reduced pressure, and was purified through silica-gel column chromatography to give 2.30 g of 2-benzyl-5-ethoxycarbonylbenzimidazole (150).

Properties of Compound (150):

^{1}H-NMR($CDCl_3$, δ): 1.39(3H, t, J=7.1 Hz), 4.26(2H, s), 4.37(2H, q, J=7.1 Hz), 7.22–7.36(5H, m), 7.50(1H, d, J=8.6 Hz), 7.94(1H, dd, J=1.5 and 8.6 Hz), 8.23(1H, d, J=1.3 Hz).

EXAMPLES 84 AND 85

Synthesis of 6-ethoxycarbonyl-2-methyl-1-(2-nitrobenzyl)benzimidazole (151) and 5-ethoxycarbonyl-2-methyl-1-(2-nitrobenzyl) benzimidazole (152)

To 1.00 g of 5-ethoxycarbonyl-2-methylbenzimidazole were added 15 ml of N,N-dimethylformamide, 1.59 g of 2-nitrobenzyl bromide and 1.23 g of sodium hydrogencarbonate, and the mixture was heated at 60° C. for 1 hour. The reaction solution was separated with the addition of 70 ml of ethyl acetate and 70 ml of water. The organic layer was then washed three times with water, and the aqueous layer was extracted three times with ethyl acetate. The resulting organic layer was concentrated under reduced pressure to obtain a mixture of 6-ethoxycarbonyl-2-methyl-1-(2-nitrobenzyl)benzimidazole and 5-ethoxycarbonyl-2-methyl-1-(2-nitrobenzyl)benzimidazole. The mixture was purified through medium-pressure silica-gel column chromatography (eluent: a mixture of hexane and ethyl acetate at a ratio of from 1:4 to 0:100) to give 0.614 g of 6-ethoxycarbonyl-2-methyl-1-(2-nitrobenzyl) benzimidazole (151) and 0.259 g of 5-ethoxycarbonyl-2-methyl-1-(2-nitrobenzyl)benzimidazole (152).

Properties of Compound (151):

^{1}H-NMR($CDCl_3$, δ): 1.38(3H, t, J=7.2 Hz), 2.56(3H, s), 4.37(2H, q, J=7.1 Hz), 5.84(2H, s), 6.41(1H, d, J=6.8 Hz), 7.44–7.53(2H, m), 7.78(1H, d, J=8.6 Hz), 7.88(1H, s), 8.02(1H, dd, J=8.3 and 1.5 Hz), 8.30(1H, dd, J=7.9 and 1.5 Hz).

Properties of Compound (152):

^{1}H-NMR($CDCl_3$, δ): 1.42(3H, t, J=7.0 Hz), 2.56(3H, s), 4.40(2H, q, J=7.0 Hz), 5.80(2H, s), 6.43(1H, dd, J=7.6 and 1.0 Hz), 7.14(1H, d, J=8.3 Hz), 7.45–7.53(2H, m), 7.95(1H,

dd, J=8.4 and 1.5 Hz), 8.27(1H, dd, J=8.0 and 1.7 Hz), 8.48(1H, d, J=1.2 Hz).

EXAMPLES 86 AND 87

Synthesis of 2-benzyl-1-(2-chlorobenzyl)-6-ethoxycarbonylbenzimidazole (153) and 2-benzyl-1-(2-chlorobenzyl)-5-ethoxycarbonylbenzimidazole (154)

In the same manner as in Examples 84 and 85, 1.06 g of 2-benzyl-1-(2-chlorobenzyl)-6-ethoxycarbonylbenzimidazole (153) and 0.640 g of 2-benzyl-1-(2-chlorobenzyl)-5-ethoxycarbonylbenzimidazole (154) were formed from 2.37 g of 2-benzyl-5-ethoxycarbonylbenzimidazole and 3.94 g of 2-chlorobenzyl bromide.

Properties of Compound (153):

^{1}H-NMR($CDCl_3$, δ): 1.83(3H, t, J=7.1 Hz), 4.23(2H, s), 4.35(2H, q, J=7.1 Hz), 5.36(2H, s), 6.23(1H, d, J=7.8 Hz), 6.97(1H, t, J=7.6 Hz), 7.11–7.45(7H, m), 7.85(1H, d, J=8.5 Hz), 7.91(1H, s), 8.02(1H, dd, J=1.2 and 8.6 Hz).

Properties of Compound (154):

^{1}H-NMR($CDCl_3$, δ): 1.41(3H, t, J=7.1 Hz), 4.25(2H, s), 4.41(2H, q, J=7.1 Hz), 5.33(2H, s), 6.22(1H, d, J=6.9 Hz), 6.97(1H, t, J=7.6 Hz), 7.12–7.28(7H, m), 7.40(1H, d, J=8.0 Hz), 7.95(1H, dd, J=1.6 and 8.6 Hz), 8.60(1H, d, J=1.4 Hz).

EXAMPLES 88 AND 89

Synthesis of 2-benzyl-1-(2,4-dichlorobenzyl)-6-ethoxycarbonylbenzimidazole (155) and 2-benzyl-1-(2,4-dichlorobenzyl)-5-ethoxycarbonylbenzimidazole (156)

In the same manner as in Examples 84 and 85, 0.49 g of 2-benzyl-1-(2,4-dichlorobenzyl)-6-ethoxycarbonylbenzimidazole and 0.52 g of 2-benzyl-1-(2,4-dichlorobenzyl)-5-ethoxycarbonylbenzimidazole (156) were formed from 2.37 g of 2-benzyl-5-ethoxycarbonylbenzimidazole and 4.45 g of 2,4-dichlorobenzyl bromide.

Properties of Compound (155):

^{1}H-NMR($CDCl_3$, δ): 1.39(3H, t), 4.24(2H, s), 4.37(2H, q), 5.32(2H, s), 6.08(1H, d, J=8.3 Hz), 6.90(1H, d, J=8.4 Hz), 7.12–7.24(5H, m), 7.41(1H, s), 7.84(1H, d, J=8.4 Hz), 7.88(1H, s), 8.03(1H, d, J=8.4 Hz).

Properties of Compound (156):

^{1}H-NMR($CDCl_3$, δ): 1.42(3H, t, J=7.1 Hz), 4.25(2H, s), 4.41(2H, q, J=7.1 Hz), 5.28(2H, s), 6.07(1H, d, J=8.4 Hz), 6.90(1H, dd, J=1.9 and 8.4 Hz), 7.08–7.28(6H, m), 7.40(1H, d, J=2.1 Hz), 7.96(1H, dd, J=1.3 and 8.3 Hz), 8.56(1H, d, J=0.9 Hz).

EXAMPLE 90

Synthesis of 5-ethoxycarbonyl-2-trifluoromethylbenzimidazole (157)

Five-percent palladium on carbon (0.50 g) was added to a solution of 4.00 g of ethyl 3-amino-4-nitro-benzoate in 100 ml of methanol, and the mixture was stirred in a hydrogen atmosphere at 50° C. for 16 hours. The solid material was separated through filtration, and the filtrate was concentrated to obtain ethyl 3,4-diaminobenzoate. Twenty milliliters of trifluoroacetic acid were added thereto, and the mixture was stirred at 60° C. for 2 hours. The reaction solution was concentrated, and chloroform was added thereto. The crystals precipitated were separated through filtration, and were dried to give 4.46 g of 5-ethoxycarbonyl-2-trifluoromethylbenzimidazole (157).

Properties of Compound (157):

^{1}H-NMR(DMSO-d6, δ): 1.36(3H, t, J=7.0 Hz), 4.36(2H, q, J=7.0 Hz), 7.82(1H, d, J=8.5 Hz), 7.99(1H, dd, J=1.5 and 8.7 Hz), 8.33(1H, s).

EXAMPLES 91 AND 92

Synthesis of 1-(biphenyl-4-ylmethyl)-6-ethoxycarbonyl-2-trifluoromethylbenzimidazole (158) and 1-(biphenyl-4-ylmethyl)-5-ethoxycarbonyl-2-trifluoromethylbenzimidazole (159)

In the same manner as in Examples 84 and 85, 0.69 g of 1-(biphenyl-4-ylmethyl)-6-ethoxycarbonyl-2-trifluoromethylbenzimidazole (158) and 0.38 g of 1-(biphenyl-4-ylmethyl)-5-ethoxycarbonyl-2-trifluoromethylbenzimidazole (159) were formed from 2.00 g of 5-ethoxycarbonyl-2-trifluoromethylbenzimidazole and 10.08 g of 4-bromomethylbiphenyl.

Properties of Compound (158):

^{1}H-NMR($CDCl_3$, δ): 1.39(3H, t), 4.38(2H, q), 5.64(2H, s), 7.18(2H, d, J=8.2 Hz), 7.34(1H, t, J=7.4 Hz), 7.42(2H, t, J=7.4 Hz), 7.52–7.57(4H, m), 7.95(1H, d, J=8.8 Hz), 8.09 (2H, dd, J=1.4 and 8.8 Hz), 8.14(1H, d, J=1.1 Hz).

Properties of Compound (159):

^{1}H-NMR($CDCl_3$, δ): 1.40(3H, t), 4.40(2H, q), 5.59(2H, s), 7.16(2H, d, J=8.1 Hz), 7.34(2H, t, J=6.2 Hz), 7.41(2H, t, J=7.5 Hz), 7.53(4H, m), 8.08(1H, dd, J=1.3 and 9.1 Hz), 8.65(1H, s).

PRODUCTION EXAMPLE 38

Production of 1-(2-chlorobenzyl)-6-hydroxymethyl-2-methylbenzimidazole

A solution of 2.66 g of 1-(2-chlorobenzyl)-6-ethoxycarbonyl-2-methylbenzimidazole in 20 ml of tetrahydrofuran was slowly added to a solution of 1.54 g of lithium aluminum hydride in 20 ml of tetrahydrofuran at a temperature of from 20 to 25° C. Further, the mixture was stirred at room temperature for 1 hour. Thirty milliliters of tetrahydrofuran were added thereto to dilute the reaction solution. Lithium ammonium hydride was decomposed and solidified with a saturated aqueous solution of sodium sulfate, and the tetrahydrofuran layer was separated. The solvent was distilled off, and the residue was purified through silica-gel column chromatography (eluent: a mixture of chloroform and methanol at a ratio of 9:1) to give 1.45 g of 1-(2-chlorobenzyl)-6-hydroxymethyl-2-methylbenzimidazole.

Properties of the compound:

^{1}H-NMR($CDCl_3$, δ): 2.53(3H, s), 4.77(2H, s), 5.39(2H, s), 6.40(1H, d, J=7.7 Hz), 7.08(1H, t, J=7.7 Hz), 7.20–7.28 (3H, m), 7.45(1H, d, J=7.9 Hz), 7.70(1H, d, JH=8.2 Hz).

PRODUCTION EXAMPLE 39

Production of 1-(biphenyl-4-ylmethyl)-6-hydroxymethyl-2-methylbenzimidazole

In the same manner as in Production Example 38, 3.72 g of 1-(biphenyl-4-ylmethyl)-6-hydroxymethyl-2-methylbenzimidazole were formed from 5.30 g of 1-(biphenyl-4-ylmethyl)-6-ethoxycarbonyl-2-methylbenzimidazole and 2.17 g of lithium aluminum hydride.

Properties of the compound:

^{1}H-NMR($CDCl_3$, δ): 2.59(3H, s), 4.78(2H, s), 5.37(2H, s), 7.11(2H, d, J=8.3 Hz), 7.24(1H, d; J=8.3 Hz), 7.30–7.37 (2H, m), 7.42(2H, t), 7.51–7.56(4H, m), 7.70(1H, d, J=8.2 Hz).

PRODUCTION EXAMPLE 40

Production of 1-(2-chlorobenzyl)-6-chloromethyl-2-methylbenzimidazole hydrochloride

Five milliliters of thionyl chloride were added to 3.56 g of 1-(2-chlorobenzyl)-6-hydroxymethyl-2-methylbenzimidazole, and the mixture was stirred at room temperature for 20 minutes and then at 80° C. for 20 minutes. After excess thionyl chloride was distilled off under reduced pressure, the residue was dissolved in 10 ml of chloroform, and the solution was crystallized from hexane. The crystals were separated through filtration, washed with hexane, and dried to give 4.07 g of 1-(2-chlorobenzyl)-6-chloromethyl-2-methylbenzimidazole hydrochloride.

Properties of the compound:

^{1}H-NMR($CDCl_3$, δ): 3.01(3H, s), 4.68(2H, s), 5.61(2H, s), 6.71(1H, d, J=7.5 Hz), 7.24–7.29(1H, m), 7.38(1H, t, J=7.7 Hz), 7.44(1H, s), 7.52(2H, d, J=8.2 Hz), 7.92(1H, d, J=8.4 Hz).

PRODUCTION EXAMPLE 41

Production of 1-(biphenyl-4-ylmethyl)-6-chloromethyl-2-methylbenzimidazole

Two milliliters of thionyl chloride were added to a solution of 3.62 g of 1-(biphenyl-4-ylmethyl)-6-hydoroxymethyl-2-methylbenzimidazole in 30 ml of chloroform at room temperature, and the mixture was stirred at 60° C. for 1 hour. A sodium hydrogencarbonate aqueous solution was added thereto to stop the reaction. The chloroform layer was washed with water, and was dried. The solvent was distilled off under reduced pressure, and the residue was crystallized from ethyl acetate. The crystals were separated through filtration, washed with ethyl acetate, and then dried to give 2.04 g of 1-(biphenyl-4-ylmethyl)-6-chloromethyl-2-methylbenzimidazole.

Properties of the compound:

^{1}H-NMR($CDCl_3$, δ): 2.67(3H, s), 4.71(2H, s), 5.40(2H, s), 7.12(2H, d, J=8.2 Hz), 7.31–7.38(3H, m), 7.43(2H, t), 7.52–7.58(4H, m), 7.75(1H, d, J=8.2 Hz).

PRODUCTION EXAMPLE 42

Production of 1-(2-chlorobenzyl)-6-formyl-2-methylbenzimidazole

Manganese dioxide (3.46 g) was added to a solution of 3.46 g of 1-(2-chlorobenzyl)-6-hydroxymethyl-2-methylbenzimidazole in 100 ml of toluene, and toluene was heat-refluxed for 3.5 hours while the mixture was dehydrated using a molecular sieve 4A. The solid material was separated through filtration, and was washed with chloroform. The filtrate was concentrated to give 3.35 g of 1-(2-chlorobenzyl)-6-formyl-2-methylbenzimidazole.

Properties of the compound:

^{1}H-NMR($CDCl_3$, δ): 2.61(3H, s), 5.48(2H, s), 6.42(1H, d, J=7.8 Hz), 7.11(1H, t, J=7.6 Hz), 7.27(1H, t), 7.48(1H, d, J=8.0 Hz), 7.76(1H, s), 7.81(1H, dd, J=1.4 and 8.3 Hz), 7.86(1H, d, J=8.3 Hz), 10.02(1H, s).

IR(KBr): 1676 cm^{-1}.

mp: 124.1–125.2° C.

PRODUCTION EXAMPLE 43

Production of 1-(2-chlorobenzyl)-2-methylbenzimidazole-6-acetonitrile

Potassium cyanate (0.450 g) and 0.450 g of 18-crown-6 were added to a solution of 1.20 g of 1-(2-chlorobenzyl)-6-chloromethyl-2-methylbenzimidazole in 10 ml of dimethylsulfoxide, and the mixture was stirred at room temperature for 18 hours. The reaction mixture was extracted with the addition of chloroform, water and a small amount of aqueous ammonia. The organic layer was concentrated, and the residue was purified through silica-gel column chromatography (eluent: a mixture of chloroform and methanol at a ratio of 20:1) to give 0.500 g of 1-(2-chlorobenzyl)-2-methylbenzimidazole-6-acetonitrile.

Properties of the compound:

^{1}H-NMR($CDCl_3$, δ): 2.52(3H, s), 3.80(2H, s), 5.37(2H, s), 6.40(1H, d, J=7.6 Hz), 7.09(1H, t), 7.10–7.19(2H, m), 7.23(1H, t), 7.44(1H, d, J=7.9 Hz), 7.70(1H, d, J=8.2 Hz).

PRODUCTION EXAMPLE 44

Production of 6-carboxy-1-(2-chlorobenzyl) benzimidazole

To 0.490 g of 4-amino-3-(2-chlorobenzyl)aminobenzoic acid formed by the method described in U.S. Pat. No. 5,294,631 were added 0.5 ml of 98% formic acid, and the mixture was refluxed for 1 hour. The solid material precipitated was collected, washed with water, and dried to give 0.468 g of 6-carboxy-1-(2-chlorobenzyl)benzimidazole.

Properties of the compound:

^{1}H-NMR(DMSO-d6, δ): 5.69(2H, s), 7.02(1H, dd, J=1.5 and 7.7 Hz), 7.30(1H, t, J=7.5 Hz), 7.36(1H, dt, J=1.7 and 7.5 Hz), 7.53(1H, dd, J=1.3 and 7.9 Hz), 7.75(1H, d, J=8.4 Hz), 7.83(1H, dd, J=1.5 and 8.4 Hz), 8.09(1H, s), 8.54(1H, s), 12.8(1H, br s).

EXAMPLE 93

Synthesis of 1-(2-chlorobenzyl)-6-ethoxycarbonyl-2-methylbenzimidazole (92)

One-hundred grams of 2-chlorobenzyl bromide were added to a solution of 86.0 g of ethyl 4-acetylamino-3-aminobenzoate and 37.3 g of potassium carbonate in 750 ml of ethanol, and the mixture was stirred at 60° C. for 14 hours. The solid material was separated through filtration, and the filtrate was concentrated to 500 ml under reduced pressure. Then, 38.7 g of 35% hydrochloric acid were added thereto, and the mixture was stirred at 60° C. for 2 hours. The solid material was separated through filtration, and the residue was neutralized with sodium hydrogencarbonate. Ethanol was distilled off under reduced pressure. The residue was extracted three times with ethyl acetate and with water. The organic layer was washed with water, and was dried. The solvent was distilled off until the amount of the organic layer reached 300 ml. The crystals precipitated were separated through filtration, and were recrystallized from ethanol to obtain 54.3 g of 1-(2-chlorobenzyl)-6-ethoxycarbonyl-2-methylbenzimidazole(192). The filtrate was also all collected, and was concentrated. The resulting crystals were recrystallized from ethanol to give 18.1 g of 1-(2-chlorobenzyl)-6-ethoxycarbonyl-2-methylbenzimidazole (92).

Properties of Compound (92):

^{1}H-NMR($CDCl_3$, δ): 1.39(3H, t, J=7.1 Hz), 2.57(3H, s), 4.37(2H, q, J=7.1 Hz), 5.46(2H, s), 6.41(1H, d, J=7.8 Hz), 7.10(1H, t, J=7.8 Hz), 7.25(1H, t), 7.47(1H, d, J=8.0 Hz), 7.75(1H, d, J=8.4 Hz), 7.94(1H, s), 8.00(1H, dd, J=1.5 and 8.4 Hz).

mp: 126.0–127.0° C.

EXAMPLE 94

Synthesis of 6-carboxy-1-(2-chlorobenzyl)-2-methylbenzimidazole (121)

To 60.0 g of 1-(2-chlorobenzyl)-6-ethoxycarbonyl-2-methylbenzimidazole were added 240 g of a 10% sodium hydroxide aqueous solution and 200 ml of ethanol, and the mixture was heat-refluxed for 2 hours. The reaction solution was cooled, and was then adjusted to a pH of 6 with 10% hydrochloric acid. The crystals precipitated were separated through filtration, and were dried to give 54.7 g of 6-carboxy-1-(2-chlorobenzyl)-2-methylbenzimidazole (121).

Properties of Compound (121):

^{1}H-NMR(DMSO-d6, δ): 2.51(3H, s), 5.62(2H, s), 6.54 (1H, d, J=7.7 Hz), 7.23(1H, t, J=7.5 Hz), 7.33(1H, t, J=7.7 Hz), 7.55(1H, d, J=8.0 Hz), 7.63(1H, d, J=8.4 Hz), 7.79(1H, d, J=8.4 Hz), 7.95(1H, s).

mp: 300.8–303.0° C.

EXAMPLE 95

Synthesis of 1-(2-chlorobenzyl)-2-methylbenzimidazole-6-acetic acid (160)

To 0.500 g of 1-(2-chlorobenzyl)-2-methylbenzimidazole-6 -acetonitrile was added 10% hydrochloric acid, and the mixture was heat-refluxed for 15 hours. The reaction mixture was neutralized with a saturated aqueous solution of sodium hydrogencarbonate, and was extracted with chloroform. The organic layer was concentrated, and was purified through silica-gel column chromatography (eluent: a mixture of chloroform and methanol at a ratio of 9:1 to 4:1) to give 0.170 g of 1-(2-chlorobenzyl)-2-methylbenzimidazole-6-acetic acid (160).

Properties of Compound (160):

^{1}H-NMR($CDCl_3$, δ): 2.42(3H, s), 3.56(2H, s), 5.15(2H, s), 6.33(1H, d), 6.96(1H, t), 7.03(1H, s), 7.13(2H, m), 7.35(1H, d, J=7.9 Hz), 7.62(1H, d), 8.90(1H, br s).

EXAMPLE 96

Synthesis of methyl 1-(2-chlorobenzyl)-2-methylbenzimidazole-6-acrylate

Methyl trifluorophosphoranilacetate (4.49 g) was added to a solution of 2.73 g of 1-(2-chlorobenzyl)-6-formyl-2-methylbenzimidazole in 50 ml of 1,4-dioxane, and the mixture was stirred for 6 hours while being heat-refluxed. After the reaction solution was cooled, the solvent was distilled off under reduced pressure, and the residue was purified through silica-gel chromatography (eluent: a mixture of chloroform and methanol at a ratio of 9:1) to obtain 7.43 g of crude methyl 1-(2-chlorobenzyl)-2-methylbenzimidazole-6-acrylate (161). This crude product was used in the subsequent reaction at once.

EXAMPLE 97

Synthesis of 1-(2-chlorobenzyl)-2-methylbenzimidazole-6-acrylic acid

The above-mentioned crude methyl 1-(2-chlorobenzyl)-2-methylbenzimidazole-6-acrylate (3.29 g) was dissolved in 20 ml of ethanol, and 10.1 g of a 5% sodium hydroxide aqueous solution were added thereto. The mixture was refluxed for 2 hours. The reaction solution was neutralized with a hydrochloric acid aqueous solution. The solvent was distilled off under reduced pressure, and the residue was purified through silica-gel chromatography (eluent: a mixture of chloroform and methanol at a ratio of from 9:1 to 6:1) to give 1.10 g of 1-(2-chlorobenzyl)-2-methylbenzimidazole-6-acrylic acid.

Properties of Compound (162):

^{1}H-NMR(DMSO-d6, δ): 2.56(3H, s), 5.65(2H, s), 6.54 (1H, d, J=15.9 Hz), 6.62(1H, d, J=7.6 Hz), 7.25(1H, t), 7.35(1H, t), 7.56(1H, d, J=8.1 Hz), 7.60–7.70(3H, m), 7.99(1H, s), 12.35(1H, br s).

EXAMPLE 98

Synthesis of 6-benzenesulfonylcarbamoyl-1-(2-chlorobenzyl)-2-methylbenzimidazole (163)

N,N'-carbonyldiimidazole (45.8 g) was added at a time to a solution of 45.0 g of 6-carboxy-1-(2-chlorobenzyl)-2-methylbenzimidazole in 950 ml of N,N-dimethylformamide, and the mixture was stirred at room temperature for 1 hour. Subsequently, 47.1 g of benzenesulfonamide and 35.0 g of diazabicycloundecene were added thereto, and the mixture was stirred at 100° C. for 70 hours. The reaction solution was cooled, and the solvent was distilled off under reduced pressure. To the residue were added 300 ml of water and 200 ml of methanol. Further, 60.7 g of 35% hydrochloric acid were added thereto to adjust the solution to a pH of 5.5. The crystals precipitated were separated through filtration, washed with 200 ml of a mixed solution of methanol and water (at a ratio of 1:1), and dried to obtain 38.4 g of 6-benzenesulfonylcarbamoyl-1-(2-chlorobenzyl)-2-methylbenzimidazole. Water was added to the filtrate. The crystals precipitated were separated through filtration, washed with water, and dried. The amount of the crystals was 13.3 g. The crystals were combined, and were dissolved by being heated with the addition of 3300 ml of acetone and 900 ml of water. From this solution, 200 ml of the solvent were distilled off while being heated, and the residue was cooled. The crystals precipitated were separated through filtration, and were dried to give 33.8 g of 6-benzenesulfonylcarbamoyl-1-(2-chlorobenzyl)-2-methylbenzimidazole (163).

Properties of Compound (163):

^{1}H-NMR(DMSO-d6, δ): 2.53(3H, s), 5.46(2H, s), 6.34 (1H, d, J=7.8 Hz), 7.11(1H, m), 7.27(1H, m), 7.48(1H, m), 7.52(2H, m), 7.60(1H, m), 7.69(1H,d, J=8.6 Hz), 7.90(1H, m), 8.09(2H, m), 8.11(1H, s), 11.84(1H, br s).

IR(KBr): 1684, 1448 cm^{-1}.

Mass(FAB): m/e 440(M+1).

mp: 273.5–274.3° C.

EXAMPLE 99

Synthesis of 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-ethylbenzimidazole (164)

In the same manner as in Example 98, 0.473 g of 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-ethylbenzimidazole (164) were formed from 0.600 g of 1-(biphenyl-4-ylmethyl)-2-ethyl-6-carboxybenzimidazole, 0.546 g of N,N'-carbonyldiimidazole, 0.529 g of benzenesulfonamide and 0.512 g of diazabicycloundecene.

Properties of Compound (164):

^{1}H-NMR(DMSO-d6, δ): 1.29(3H, t, J=7.4 Hz), 2.88(2H, q, J=7.4 Hz), 5.59(2H, s), 7.16(2H, d, J=8.2 Hz), 7.33–7.37 (1H, m), 7.44(2H, t, J=7.5 Hz), 7.59–7.71(8H, m), 7.74(1H, dd, J=8.4 and 1.4 Hz), 7.98–8.02(2H, m), 8.21(1H, s), 12.43(1H, s).

IR(KBr): 1684 cm^{-1}.

mp: 149.5–157.0° C.

EXAMPLE 100

Synthesis of 5-benzenesulfonylcarbamoyl-1-(2-chlorobenzyl)-2-methylbenzimidazole (165)

In the same manner as in Example 98, 0.480 g of 5-benzenesulfonylcarbamoyl-1-(2-chlorobenzyl)-2-methylbenzimidazole (165) were formed from 0.450 g of 5-carboxy-1-(2-chlorobenzyl)-2-methylbenzimidazole, 0.485 g of N,N'-carbonyldiimidazole, 0.470 g of benzenesulfonamide and 0.456 g of diazabicycloundecene.

Properties of Compound (165):

^{1}H-NMR(DMSO-d6, δ): 2.53(3H, s), 5.61(2H, s), 6.57 (1H, d, J=7.4 Hz), 7.22(1H, t), 7.33(1H, t), 7.50(1H, d, J=8.6 Hz), 7.54(1H, dd, J=7.9 and 0.9 Hz), 7.63(2H, t), 7.71(2H, m), 8.00(2H, d, J=7.3 Hz), 8.21(1H, d, J=1.4 Hz), 12.50(1H, br s).

IR(KBr): 1685 cm^{-1}.

mp: 137.0–138.5° C.

EXAMPLE 101

Synthesis of 5-(4-chlorobenzenesulfonylcarbamoyl)-1-(2-chlorobenzyl)-2-methylbenzimidazole (166)

In the same manner as in Example 98, 0.520 g of 5-(4-chlorobenzenesulfonylcarbamoyl)-1-(2-chlorobenzyl)-2-methylbenzimidazole (166) were formed from 0.450 g of 5-carboxy-1-(2-chlorobenzyl)-2-methylbenzimidazole, 0.485 g of N,N'-carbonyldiimidazole, 0.573 g of 4-chlorobenzenesulfonamide and 0.456 g of diazabicycloundecene.

Properties of Compound (166):

^{1}H-NMR(DMSO-d6, δ): 2.49(3H, s), 5.58(2H, s), 6.51 (1H, d, J=7.6 Hz), 7.21(1H, t), 7.32(1H, t), 7.45(1H, d, J=8.6 Hz), 7.53(1H, d, J=7.8 Hz), 7.69(3H, d, J=8.6 Hz), 7.99(2H, d, J=8.6 Hz), 8.18(1H, s), 12.58(1H, br s).

IR(KBr): 1619 cm^{-1}.

mp: 261.5–263.0° C.

EXAMPLE 102

Synthesis of 1-(2-chlorobenzyl)-2-methyl-5-(2-naphthalenesulfonylcarbamoyl)benzimidazole (167)

In the same manner as in Example 98, 0.352 g of 1-(2-chlorobenzyl)-2-methyl-5-(2-naphthalenesulfonylcarbamoyl)benzimidazole (167) were formed from 0.450 g of 5-carboxy-1-(2-chlorobenzyl)-2-methylbenzimidazole, 0.485 g of N,N'-carbonyldiimidazole, 0.620 g of 2-naphthalenesulfonamide and 0.456 g of diazabicycloundecene.

Properties of Compound (167):

^{1}H-NMR(DMSO-d6, δ): 2.48(3H, s), 5.56(2H, s), 6.49 (1H, d, J=7.7 Hz), 7.20(1H, t, J=7.6 Hz), 7.31(1H, t, J=7.7 Hz), 7.44(1H, d, J=8.6 Hz), 7.52(1H, d, J=8.0 Hz), 7.66–7.75(3H, m), 7.97(1H, d, J=8.8 Hz), 8.04(1H, d, J=8.0 Hz), 8.14(1H, d, J=8.8 Hz), 8.19(1H, s), 8.23(1H, d, J=8.0 Hz), 8.68(1H, s), 12.55(1H, br s).

IR(KBr): 1685 cm^{-1}.

mp: 236.5–238.0° C.

EXAMPLE 103

Synthesis of 1-(2-chlorobenzyl)-6-methanesulfonylcarbamoyl-2-methylbenzimidazole (168)

In the same manner as in Example 98, 0.564 g of 1-(2-chlorobenzyl)-6-methanesulfonylcarbamoyl-2-methylbenzimidazole (168) were formed from 0.500 g of 6-carboxy-1-(2-chlorobenzyl)-2-methylbenzimidazole, 0.539 g of N,N'-carbonyldiimidazole, 0.316 g of methanesulfonamide and 0.506 g of diazabicycloundecene.

Properties of Compound (168):

^{1}H-NMR(DMSO-d6, δ): 2.49(3H, s), 3.35(3H, s), 5.60 (2H, s), 6.43(1H, d, J=7.8 Hz), 7.23(1H, t), 7.34(1H, t, J=7.7 Hz), 7.57(1H, d, J=8.0 Hz), 7.68(1H, d, J=8.5 Hz), 7.81(1H, dd, J=1.7 and 8.5 Hz), 8.13(1H, d, J=1.5 Hz), 11.94(1H, br s).

IR(KBr): 1670 cm^{-1}.

mp: 302.0–303.0° C.

EXAMPLE 104

Synthesis of 6-(1-butanesulfonylcarbamoyl)-1-(2-chlorobenzyl)-2-methylbenzimidazole (169)

In the same manner as in Example 98, 0.595 g of 6-(1-butanesulfonylcarbamoyl)-1-(2-chlorobenzyl)-2-methylbenzimidazole (169) were formed from 0.500 g of 6-carboxy-1-(2-chlorobenzyl)-2-methylbenzimidazole, 0.539 g of N,N'-carbonyldiimidazole, 0.456 g of 1-butanesulfonamide and 0.506 g of diazabicycloundecene.

Properties of Compound (169):

^{1}H-NMR(DMSO-d6, δ): 0.84(3H, t, J=7.4 Hz), 1.38(2H, m), 1.65(2H, m), 2.49(3H, s), 3.49(2H, m), 5.60(2H, s), 6.44(1H, d, J=7.6 Hz), 7.23(1H, t, J=7.6 Hz), 7.35(1H, t), 7.56(1H, d, J=8.0 Hz), 7.68(1H, d, J=8.4 Hz), 7.80(1H, dd, J=1.6 and 8.4 Hz), 8.11(1H, d, J=1.4 Hz), 11.86(1H, br s).

IR(KBr): 1684 cm^{-1}.

mp: 214.0–217.0° C.

EXAMPLE 105

Synthesis of 1-(2-chlorobenzyl)-2-methyl-6-(1-octanesulfonylcarbamoyl)benzimidazole (170)

In the same manner as in Example 98, 0.309 g of 1-(2-chlorobenzyl)-2-methyl-6-(1-octanesulfonylcarbamoyl)benzimidazole (170) were formed from 0.400 g of 6-carboxy-1-(2-chlorobenzyl)-2-methylbenzimidazole, 0.431 g of N,N'-carbonyldiimidazole, 406 g of 1-octanesulfonamide and 0.404 g of diazabicycloundecene.

Properties of Compound (170):

^{1}H-NMR(DMSO-d6, δ): 0.82(3H, t, J=7.3 Hz), 1.13–1.28 (8H, m), 1.32–1.41(2H, m), 1.62–1.71(2H, m), 2.50(3H, s), 3.50(2H, t, J=8.5 Hz), 5.61(2H, s), 6.45(1H, d, J=7.7 Hz), 7.24(1H, t, J=7.5 Hz), 7.35(1H, t, J=7.5 Hz), 7.58(1H, d, J=8.0 Hz), 7.69(1H, d, J=8.4 Hz), 7.81(1H, d, J=8.5 Hz), 8.12(1H, s), 11.86(1H ,s).

IR(KBr): 1674 cm^{-1}.

mp: 180.0–183.0° C.

EXAMPLE 106

Synthesis of 1-(2-chlorobenzyl)-2-methyl-6-(2-propanesulfonylcarbamoyl)benzimidazole (171)

In the same manner as in Example 98, 0.417 g of 1-(2-chlorobenzyl)-2-methyl-6-(2-

propanesulfonylcarbamoyl)benzimidazole (171) were formed from 0.400 g of 6-carboxy-1-(2-chlorobenzyl)-2-methylbenzimidazole, 0.431 g of N,N'-carbonyldiimidazole, 0.328 g of 2-propanesulfonamide and 0.404 g of diazabicycloundecene.

Properties of Compound (171):

^{1}H-NMR(DMSO-d6, δ): 1.30(6H, d, J=6.9 Hz), 2.50(3H, s), 3.81–3.87(1H, m), 5.62(2H, s), 6.46(1H, d, J=7.7 Hz), 7.25(1H, t, J=7.5 Hz), 7.35(1H, t, J=7.5 Hz), 7.62(1H, d, J=7.9 Hz), 7.69(1H, d, J=8.5 Hz), 7.81(1H, d, J=8.6 Hz), 8.12(1H, s), 11.83(1H, s).

IR(KBr): 1670 cm^{-1}.

mp: 215.0–217.5° C.

EXAMPLE 107

Synthesis of 1-(biphenyl-4-ylmethyl)-6-(1-butanesulfonylcarbamoyl)-2-methylbenzimidazole (172)

In the same manner as in Example 98, 0.349 g of 1-(biphenyl-4-ylmethyl)-6-(1-butanesulfonylcarbamoyl)-2-methylbenzimidazole (172) were formed from 0.300 g of 1-(biphenyl-4-ylmethyl)-6-carboxy-2-methylbenzimidazole, 0.323 g of N,N'-carbonyldiimidazole, 0.273 g of 1-butanesulfonamide and 0.303 g of diazabicycloundecene.

Properties of Compound (172)

^{1}H-NMR(DMSO-d6, δ): 0.85(3H, t, J=7.4 Hz), 1.36–1.43 (2H, m), 1.63–1.72(2H, m), 2.57(3H, s), 3.52(2H, t, J=7.7 Hz), 5.60(2H, s), 7.21(2H, d, J=8.2 Hz), 7.35(1H, t, J=7.3 Hz), 7.44(2H, t, J=7.5 Hz), 7.60–7.68(5H, m), 7.81(1H, dd, J=1.6 and 8.4 Hz), 8.26(1H, d, J=1.4 Hz), 11.97(1H, s).

IR(KBr): 1676 cm^{-1}.

mp: 219.5–222.5° C.

EXAMPLE 108

Synthesis of 6-(1-butanesulfonylcarbamoyl)-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole (173)

In the same manner as in Example 98, 0.459 g of 6-(1-butanesulfonylcarbamoyl)-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole (173) were formed from 0.400 g of 6-carboxy-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole, 0.431 g of N,N'-carbonyldiimidazole, 0.364 g of 1-butanesulfonamide and 0.404 g of diazabicycloundecene.

Properties of Compound (173):

^{1}H-NMR(DMSO-d6, δ): 0.85(3H, t, J=7.3 Hz), 1.36–1.42 (2H, m), 1.63–1.70(2H, m), 2.50(3H, s), 3.51(2H, t, J=7.7 Hz), 5.59(2H, s), 6.45(1H, d, J=8.4 Hz), 7.33(1H, dd, J=2.1 and 8.4 Hz), 7.69(1H, d, J=8.4 Hz), 7.76(1H, d, J=2.0 Hz), 7.81(1H, dd, J=1.7 and 8.5 Hz), 8.11(1H, d, J=1.3 Hz), 11.90(1H, s).

IR(KBr): 1670 cm^{-1}.

mp: 222.0–223.0° C.

EXAMPLE 109

Synthesis of 1-(biphenyl-4-ylmethyl)-6-(1-butanesulfonylcarbamoyl)- 2-ethylbenzimidazole (174)

In the same manner as in Example 98, 0.300 g of 1-(biphenyl-4-ylmethyl)-6-(1-butanesulfonylcarbamoyl)-2-ethylbenzimidazole (174) were formed from 0.300 g of 1-(biphenyl-4-ylmethyl)-6-carboxy-2-ethylbenzimidazole, 0.340 g of N,N'-carbonyldiimidazole, 0.300 g of butanesulfonamide and 0.320 g of diazabicycloundecene.

Properties of Compound (174):

^{1}H-NMR(DMSO-d6, δ): 0.85(3H, t, J=7.3 Hz), 1.30(3H, t, J=7.5 Hz), 1.35–1.44(2H, m), 1.64–1.72(2H, m), 2.90(2H, q, J=7.4 Hz), 3.52(2H, t, J=7.7 Hz), 5.61(2H, s), 7.19(2H, d, J=8.3 Hz), 7.35(1H, t, J=7.3 Hz), 7.44(2H, t, J=7.5 Hz), 7.61–7.67(4H, m), 7.71(1H, d, J=8.5 Hz), 7.82(1H, dd, J=1.6 and 8.5 Hz), 8.27(1H, d, J=1.3 Hz), 12.01(1H, s). IR(Nujol): 1687,1682 cm^{-1}.

mp: 171.8–173.0° C.

EXAMPLE 110

Synthesis of 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-trifluoromethylbenzimidazole (175)

In the same manner as in Example 98, 0.508 g of 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-trifluoromethylbenzimidazole (175) were formed from 0.483 g of 1-(biphenyl-4-ylmethyl)-6-carboxy-2-trifluoromethylbenzimidazole, 0.396 g of N,N'-carbonyldiimidazole, 0.383 g of benzenesulfonamide and 0.371 g of diazabicycloundecene.

Properties of Compound (175):

^{1}H-NMR(DMSO-d6, δ): 5.81(2H, s), 7.15(2H, d, J=8.3 Hz), 7.35(1H, t, J=7.5 Hz), 7.44(2H, t, J=7.5 Hz), 7.60–7.66 (6H, m), 7.70(1H, t, J=7.4 Hz), 7.91(1H, dd, J=8.7 and 1.4 Hz), 7.96–8.01(3H, m), 8.42(1H, s), 12.65(1H, s).

IR(KBr): 1685 cm^{-1}.

mp: 164.5–167.0° C.

EXAMPLE 111

Synthesis of 5-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-trifluoromethylbenzimidazole (176)

In the same manner as in Example 98, 0.286 g of 5-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-trifluoromethylbenzimidazole (176) were formed from 0.270 g of 1-(biphenyl-4-ylmethyl)-5-carboxy-2-trifluoromethylbenzimidazole, 0.221 g of N,N'-carbonyldiimidazole, 0.214 g of benzenesulfonamide and 0.207 g of diazabicycloundecene.

Properties of Compound (176):

^{1}H-NMR(DMSO-d6, δ): 5.79(2H, s), 7.15(2H, d, J=8.1 Hz), 7.35(1H, t, J=7.5 Hz), 7.43(2H, t, J=7.5 Hz), 7.59–7.67 (6H, m), 7.72(1H, t, J=7.6 Hz), 7.83(1H, d, J=8.8 Hz), 7.94(1H, d, J=8.9 Hz), 8.02(2H, d, J=7.4 Hz), 8.49(1H, s), 12.69(1H, s).

IR(KBr): 1699 cm^{-1}.

mp: 248.5–251.0° C.

EXAMPLE 112

Synthesis of 6-benzenesulfonylcarbamoyl-2-cyclopropyl-1-(2-fluorobenzyl)benzimidazole (177)

In the same manner as in Example 98, 0.730 g of 6-benzenesulfonylcarbamoyl-2-cyclopropyl-1-(2-fluorobenzyl)benzimidazole (177) were formed from 0.930 g of 6-carboxy-2-cyclopropyl-1-(2-fluorobenzyl) benzimidazole, 0.972 g of N,N'-carbonyldiimidazole, 0.942 g of benzenesulfonamide and 0.906 g of diazabicycloundecene.

Properties of Compound (177):

^{1}H-NMR (DMSO-d6, δ): 1.04 (4H, m), 2.15 (1H, m), 5.70 (2H, s), 6.85 (1H, t, J=7.5 Hz), 7.12 (1H, t, J=7.5 Hz), 7.22–7.38 (2H, m), 7.54–7.70 (5H, m), 7.99 (2H, d, J=7.5 Hz), 8.11 (1H, s).

white powder.

EXAMPLE 113

Synthesis of N-benzenesulfonyl-3-1-(2-chlorobenzyl)-2-methylbenzimidazol-6-yl] acrylamide (178)

In the same manner as in Example 98, 1.05 g of N-benzenesulfonyl-3-[1-(2-chlorobenzyl)-2-methylbenzimidazol-6-yl]acrylamide (178) were formed from 1.10 g of 1-(2-chlorobenzyl)-2-methylbenzimidazole-6-acrylic acid, 1.09 g of N,N'-carbonyldiimidazole, 1.06 g of benzenesulfonamide and 1.02 g of diazabicycloundecene.

Properties of Compound (178):

^{1}H-NMR(DMSO-d6, δ): 2.47(3H ,s), 5.55(2H, s), 6.46–6.55(2H, m), 7.22(1H, t, J=7.6 Hz), 7.32(1H, t, J=7.7 Hz), 7.40(1H, d, J=8.4 Hz), 7.52–7.66(6H, m), 7.69(1H, t), 7.93(2H, d, J=7.9 Hz), 12.17(1H, br s).

IR(KBr): 1687 cm^{-1}.

Mass(FAB): m/e 466(M+1).

mp: 243.1–244.3° C.

EXAMPLE 114

Synthesis of N-benzenesulfonyl-2-[1-(2-chlorobenzyl)-2-methylbenzimidazol-6-yl]acetamide (179)

In the same manner as in Example 98, 0.09 g of N-benzenesulfonyl-2-[1-(2-chlorobenzyl)-2-methylbenzimidazol-6-yl]acetamide (179) were formed from 0.170 g of 1-(2-chlorobenzyl)-2-methylbenzimidazole-6-acetic acid, 0.175 g of N,N'-carbonyldiimidazole, 0.170 g of benzenesulfonamide and 0.164 g of diazabicycloundecene.

Properties of Compound (179):

^{1}H-NMR(DMSO-d6, δ): 2.44(3H, s), 3.57(2H, s), 5.46 (2H, s), 6.41(1H, d, J=7.7 Hz), 6.96(1H, d, J=7.0 Hz), 7.16(1H, s), 7.20(1H, t), 7.32(1H, t), 7.47(1H, d, J=8.2 Hz), 7.52–7.59(3H, m), 7.67(1H, t, J=7.5 Hz), 7.84(2H, d, J=7.4 Hz), 12.28(1H, br s).

IR(KBr) 1719 cm^{-1}.

mp: 236.2–237.8° C.

EXAMPLE 115

Synthesis of 1-(2,4-dichlorobenzyl)-2-methyl-6-[(2-pyridylmethyl)carbamoyl]benzimidazole (180)

Dichloromethane (150 ml) and some drops of N,N-dimethylformamide were added to 9.00 g of 6-carboxy-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole, and the mixture was cooled with ice. Oxalyl chloride (6.84 g) were added dropwise thereto, and the mixed solution was stirred for some minutes. Further, this solution was stirred at room temperature for 1.5 hours, and was then concentrated to a volume of approximately ⅓ of the original volume under reduced pressure. The solid material precipitated was collected, and was added to a solution of 2.69 g of 2-aminomethylpyridine and 7.34 g of triethylamine in 200 ml of dichloromethane in some divided portions. After the mixture was stirred for 15 hours, the reaction solution was washed three times with water and then with a saturated aqueous solution of sodium hydrogencarbonate. The organic layer was concentrated under reduced pressure, and was crystallized from ethyl acetate. The crystals were separated through filtration, and were dried to give 4.35 g of 1-(2,4-dichlorobenzyl)-2-methyl-6-[(2-pyridylmethyl)carbamoyl] benzimidazole (180).

Properties of Compound (180):

^{1}H-NMR($CDCl_3$, δ): 2.56(3H, s), 4.76(2H, d, J=4.8 Hz), 5.40(2H, s), 6.33(1H, d, J=8.4 Hz), 7.07(1H, dd, J=8.4 and 2.0 Hz), 7.22(1H, dd, J=7.4 and 4.9 Hz), 7.33(1H, d, J=7.9 Hz), 7.48(1H, d, J=2.1 Hz), 7.62–7.79(4H, m), 7.86(1H, d, J=1.1 Hz)8.57, (1H, d, J=4.9 Hz).

IR(KBr): 1645 cm^{-1}.

mp: 204.5–206.5° C.

EXAMPLE 116

Synthesis of 1-methyl-2-n-propyl-6-[(2-pyridylmethyl)carbamoyl]benzimidazole (181)

In the same manner as in Example 115, 0.213 g of 1-methyl-2-n-propyl-6-[(2-pyridylmethyl)carbamoyl] benzimidazole (181) were formed from 0.402 g of 6-carboxy-1-methyl-2-n-propylbenzimidazole, 0.468 g of oxalyl chloride, 0.199 g of 2-aminomethylpyridine and 0.559 g of triethylamine.

Properties of Compound (181):

^{1}H-NMR($CDCl_3$, δ): 1.08(3H, t, J=7.4 Hz) 1.92(2H, m) 2.88(2H, m) 3.76(3H, s) 4.80(2H, d, J=4.8 Hz), 7.22(1H, dd, J=2.5 and 7.5 Hz), 7.35(1H, d, J=7.8 Hz), 7.67–7.77(4H, m), 7.80(1H, s), 8.58(1H, dd, J=4.9 and 0.9 Hz).

IR(KBr): 1647 cm^{-1}.

mp: 140.5–141.5° C.

EXAMPLE 117

Synthesis of 1-(2-chlorobenzyl)-2-methyl-6-[(2-pyridylmethyl)carbamoyl]benzimidazole (182)

In the same manner as in Example 115, 0.164 g of 1-(2-chlorobenzyl)-2-methyl-6-[(2-pyridylmethyl) carbamoyl]benzimidazole (182) were formed from 0.300 g of 6-carboxy-1-(2-chlorobenzyl)-2-methylbenzimidazole, 0.253 g of oxalyl chloride, 0.108 g of 2-aminomethylpyridine and 0.302 g of triethylamine.

Properties of Compound (182):

^{1}H-NMR($CDCl_3$, δ): 2.56(3H, s), 4.76(2H, d, J=4.8 Hz), 5.45(2H, s), 6.40(1H, d, J=7.8 Hz), 7.08(1H, t, J=7.6 Hz), 7.20–7.27(2H, m), 7.33(1H, d, J=7.8 Hz), 7.45(1H, dd, J=0.9 and 8.1 Hz), 7.64(1H, s), 7.65–7.69(1H, m), 7.72(1H, dd, J=1.5 and 8.4 Hz), 7.77(1H, d, J=8.4 Hz), 7.88(1H, d, J=1.2 Hz), 8.56(1H, d, J=4.7 Hz).

IR(KBr): 1646 cm^{-1}.

mp: 156.5–157.5° C.

EXAMPLE 118

Synthesis of 2-n-propyl-1-i-propyl-6-[(2-pyridylmethyl)carbamoyl]benzimidazole (183)

In the same manner as in Example 115, 0.020 g of 2-n-propyl-1-i-propyl-6-[(2-pyridylmethyl)carbamoyl] benzimidazole (183) were formed from 0.095 g of 6-carboxy-2-n-propyl-1-i-propylbenzimidazole, 0.100 g of oxalyl chloride, 0.039 g of 2-aminomethylpyridine and 0.097 g of triethylamine.

Properties of Compound (183):

^{1}H-NMR($CDCl_3$, δ): 1.08(3H, t, J=7.4 Hz), 1.69(6H, d, J=7.1 Hz), 1.87–1.93(2H, m), 2.90(2H, t, J=7.8 Hz), 4.69–4.75(1H, m), 4.80(2H, d, J=4.9 Hz), 7.23(1H, dd, J=7.3 and 2.1 Hz), 7.37(1H, d, J=7.7 Hz), 7.62–7.77(4H, m), 8.21(1H, s), 8.58(1H, d, J=4.5 Hz).

IR(KBr): 1631 cm^{-1}.

mp: 155.0–156.9° C.

EXAMPLE 119

Synthesis of 1-n-butyl-2-n-propyl-6-[(2-pyridylmethyl)carbamoyl]benzimidazole (184)

In the same manner as in Example 115, 0.283 g of 1-n-butyl-2-n-propyl-6-[(2-pyridylmethyl)carbamoyl] benzimidazole (184) were formed from 0.500 g of 1-n-butyl-6-carboxy-2-n-propylbenzimidazole, 0.487 g of oxalyl chloride, 0.208 g of 2 -aminomethylpyridine and 0.582 g of triethylamine.

Properties of Compound (184):

^{1}H-NMR($CDCl_3$, δ): 0.97(3H, t, J=7.3 Hz), 1.08(3H, t, J=7.4 Hz), 1.37–1.46(2H, m), 1.76–1.83(2H, m), 1.92–2.00 (2H, m), 2.86(2H, t, J=7.8 Hz), 4.15(2H, t, J=7.6 Hz), 4.81(2H, d, J=4.8 Hz), 7.23(1H, dd, J=7.3 and 2.4 Hz), 7.36(1H, d, J=7.8 Hz), 7.63–7.76(4H, m), 8.02(1H, s), 8.58(1H, d, J=4.7 Hz).

IR(KBr): 1631 cm^{-1}.

mp: 105.8–107.2° C.

EXAMPLE 120

Synthesis of 1-(3-chlorobenzyl)-2-n-propyl-6-[2-pyridylmethyl)carbamoyl]benzimidazole (185)

In the same manner as in Example 115, 0.311 g of 1-(3-chlorobenzyl)-2-n-propyl-6-[2-pyridylmethyl) carbamoyl]benzimidazole (185) were formed from 0.580 g of 6-carboxy-1-(3-chlorobenzyl)-2-n-propylbenzimidazole, 0.407 g of oxalyl chloride, 0.173 g of 2-aminomethylpyridine and 0.486 g of triethylamine.

Properties of Compound (185):

^{1}H-NMR($CDCl_3$, δ): 1.03(3H, t, J=7.4 Hz), 1.85–1.93 (2H, m), 2.80(2H, t, J=7.5 Hz), 4.77(2H, d, J=4.8 Hz), 5.36(2H, s), 6.86(1H, d, J=7.4 Hz), 7.02(1H, s), 7.20–7.28 (3H, m), 7.33(1H, d, J=7.8 Hz), 7.63–7.73(3H, m), 7.79(1H, d, J=8.4 Hz), 7.91(1H, d, J=1.3 Hz), 8.57(1H, d, J=4.7 Hz).

IR(KBr): 1643 cm^{-1}.

mp: 157.7–158.8° C.

EXAMPLE 121

Synthesis of 1-benzyl-2-n-propyl-6-[(2-pyridylmethyl)carbamoyl]benzimidazole (186)

In the same manner as in Example 115, 0.350 g of 1-benzyl-2-n-propyl-6-[(2-pyridylmethyl)carbamoyl] benzimidazole (186) were formed from 0.850 g of 1-benzyl-6-carboxy-2-n-propylbenzimidazole, 0.949 g of oxalyl chloride, 0.404 g of 2-aminomethylpyridine and 1.132 g of triethylamine.

Properties of Compound (186):

^{1}H-NMR($CDCl_3$, δ): 1.01(3H, t, J=7.4 Hz), 1.83–1.92 (2H, m), 2.82(2H, t, J=7.6 Hz), 4.77(2H, d, J=4.8 Hz), 5.40(2H, s), 7.03(2H, d, J=6.5 Hz), 7.21(1H, dd, J=7.1 and 2.1 Hz), 7.18–7.34(4H, m), 7.60(1H, s), 7.65–7.72(2H, m), 7.78(1H, d, J=8.4 Hz), 7.94(1H, d, J=1.2 Hz), 8.56(1H,d,J= 4.2 Hz).

IR(KBr): 1642 cm^{-1}.

mp: 121.9–123.1° C.

EXAMPLE 122

Synthesis of 1-(4-chlorobenzyl)-2-propyl-6-[(2-pyridylmethyl)carbamoyl]benzimidazole (187)

In the same manner as in Example 115, 0.089 g of 1-(4-chlorobenzyl)-2-propyl-6-[(2-pyridylmethyl) carbamoyl]benzimidazole (187) were formed from 0.547 g of 6-carboxy-1-(4-chlorobenzyl)-2-propylbenzimidazole, 0.384 g of oxalyl chloride, 0.163 g of 2-aminomethylpyridine and 0.458 g of triethylamine.

Properties of Compound (187):

^{1}H-NMR($CDCl_3$, δ): 1.02(3H, t, J=7.4 Hz), 1.84–1.92 (2H, m), 2.77–2.83(2H, m), 4.76(2H, d, J=4.8 Hz), 5.36(2H, s), 6.96(2H, d, J=8.3 Hz), 7.22(1H, dd, J=6.4 and 0.4 Hz), 7.27(2H, dd, J=8.3 and 1.3 Hz), 7.33(1H, d, J=7.8 Hz), 7.62–7.73(3H, m), 7.78(1H, d, J=8.4 Hz), 7.91(1H, d, J=0.9 Hz), 8.56(1H, dd, J=4.9 and 0.8 Hz).

IR(KBr): 1643 cm^{-1}.

mp: 158.8–161.0° C.

EXAMPLE 123

Synthesis of 2-benzyl-1-methyl-6-[(2-pyridylmethyl)carbamoyl]benzimidazole (188)

In the same manner as in Example 115, 0.171 g of 2-benzyl-1-methyl-6-[(2-pyridylmethyl)carbamoyl] benzimidazole (188) were formed from 0.310 g of 2-benzyl-6-carboxy-1-methylbenzimidazole, 0.295 g of oxalyl chloride, 0.108 g of 2-aminomethylpyridine and 0.303 g of triethylamine.

Properties of Compound (188):

^{1}H-NMR($CDCl_3$, δ): 3.66(3H, s), 4.35(2H, s), 4,80(2H, d, J=4.8 Hz), 7.21–7.37(7H, m), 7.66(1H, br t), 7.67–7.73(2H, m), 7.78(1H, d, J=8.4 Hz), 7.98(1H, s), 8.58(1H, d, J=4.9 Hz).

IR(KBr): 1632 cm^{-1}.

mp: 168.5–169.5° C.

EXAMPLE 124

Synthesis of 1-(2,6-dichlorobenzyl)-2-methyl-6-[(2-pyridylmethyl)carbamoyl]benzimidazole (189)

In the same manner as in Example 115, 0.040 g of 1-(2,6-dichlorobenzyl)-2-methyl-6-[(2-pyridylmethyl) carbamoyl]benzimidazole (189) were formed from 0.600 g of 6-carboxy-1-(2,6-dichlorobenzyl)-2-methylbenzimidazole, 0.472 g of oxalyl chloride, 0.201 g of 2-aminomethylpyridine and 0.188 g of triethylamine.

Properties of Compound (189):

^{1}H-NMR($CDCl_3$, δ): 2.62(3H, s), 4.76(2H, d, J=4.7 Hz), 5.62(2H, s), 7.23(1H, dd, J=7.1 and 2.2 Hz), 7.28(1H, d, J=7.8 Hz), 7.32(1H, d, J=7.9 Hz), 7.39(2H, d, J=8.1 Hz), 7.54(1H, s), 7.66–7.71(3H, m), 7.78(1H, s), 8.60(1H, d, J=4.6 Hz).

IR(KBr): 1635 cm^{-1}.

mp: 225.7–226.9° C.

EXAMPLE 125

Synthesis of 2-methyl-6-[(2-pyridylmethyl) carbamoyl]-1-[2-(trifluoromethyl)benzyl] benzimidazole (190)

In the same manner as in Example 115, 0.713 g of 2-methyl-6-[(2-pyridylmethyl)carbamoyl]-1-[2-

(trifluoromethyl)benzyl]benzimidazole (190) were formed from 0.970 g of 6-carboxy-2-methyl-1-[2-(trifluoromethyl) benzyl]benzimidazole, 0.736 g of oxalyl chloride, 0.261 g of 2-aminomethylpyridine and 0.726 g of triethylamine.

Properties of Compound (190):

^{1}H-NMR($CDCl_3$, δ): 2.54(3H, s), 4.76(2H, d, J=4.8 Hz), 5.59(2H, s), 6.45(1H, d, J=7.9 Hz), 7.22(1H, t, J=5.8 Hz), 7.34(2H, t, J=8.8 Hz), 7.40(1H, t, J=7.5 Hz), 7.62(1H, br s), 7.68(1H, dt, J=1.7 and 7.7 Hz), 7.72–7.82(3H, m), 7.87(1H, s), 8.56(1H, d, J=4.9 Hz).

IR(KBr): 1648 cm^{-1}.

mp: 172–174° C.

EXAMPLE 126

Synthesis of 2-methyl-6-[(2-pyridylmethyl) carbamoyl]-1-[4-(trifluoromethyl)benzyl] benzimidazole (191)

In the same manner as in Example 115, 0.194 g of 2-methyl-6-[(2-pyridylmethyl)carbamoyl]-1-[4-(trifluoromethyl)benzyl]benzimidazole (191) were formed from 0.970 g of 6-carboxy-2-methyl-1-[4-(trifluoromethyl) benzyl]benzimidazole, 0.736 g of oxalyl chloride, 0.261 g of 2-aminomethylpyridine and 0.726 g of triethylamine.

Properties of Compound (191):

^{1}H-NMR($CDCl_3$, δ): 2.59(3H, s), 4.77(2H, d, J=4.7 Hz), 5.45(2H, s), 7.15(2H, d, J=8.2 Hz), 7.23(1H, m), 7.33(1H, d, J=7.9 Hz), 7.58(2H, d, J=8.2 Hz), 7.63(1H, br s), 7.67–7.74 (2H, m), 7.77(1H, d, J=8.3 Hz), 7.93(1H, s), 8.57(1H, d, J=4.9 Hz).

IR(KBr): 1637 cm^{-1}.

mp: 188.5–190.0° C.

EXAMPLE 127

Synthesis of 1-(3,4-dichlorobenzyl)-2-methyl-6-[(2-pyridylmethyl)carbamoyl]benzimidazole (192)

In the same manner as in Example 115, 0.264 g of 1-(3,4-dichlorobenzyl)-2-methyl-6-[(2-pyridylmethyl) carbamoyl]benzimidazole (192) were formed from 0.500 g of 6-carboxy-1-(3,4-dichlorobenzyl)-2-methylbenzimidazole, 0.393 g of oxalyl chloride, 0.167 g of 2-aminomethylpyridine and 0.469 g of triethylamine.

Properties of Compound (192):

^{1}H-NMR($CDCl_3$, δ): 2.58(3H, s), 4.77(2H, d, J=4.8 Hz), 5.33(2H, s), 6.85(1H, dd, J=8.3 and 2.2 Hz), 7.14(1H, d, J=2.1 Hz), 7.22(1H, dd, J=7.3 and 5.6 Hz), 7.33(1H, d, J=7.8 Hz), 7.38(1H, d, J=8.3 Hz), 7.65–7.77(4H, m), 7.92(1H, d, J=1.2 Hz), 8.57(1H, d, J=4.8 Hz).

IR(KBr): 1638 cm^{-1}.

mp: 219.0–220.7° C.

EXAMPLE 128

Synthesis of 2-methyl-1-(2-methylbenzyl)-6-[(2-pyridylmethyl)carbamoyl]benzimidazole (193)

In the same manner as in Example 115, 0.100 g of 2-methyl-1-(2-methylbenzyl)-6-[(^{2}-pyridylmethyl) carbamoyl]benzimidazole (193) were formed from 0.453 g of 6-carboxy-2-methyl-1-(2-methylbenzyl)benzimidazole, 0.411 g of oxalyl chloride, 0.175 g of 2-aminomethylpyridine and 0.490 g of triethylamine.

Properties of Compound (193):

^{1}H-NMR($CDCl_3$, δ): 2.42(3H, s), 2.54(3H, s), 4.75(2H, d, J=4.9 Hz), 5.32(2H, s), 6.33(1H, d, J=7.8 Hz), 7.01(1H, t, J=7.8 Hz), 7.17–7.24(3H, m), 7.33(1H, d, J=7.8 Hz), 7.60 (1H, s), 7.63–7.73(2H, m), 7.76(1H, d, J=8.4 Hz), 7.84(1H, d, J=1.4 Hz), 8.56(1H, d, J=4.9 Hz).

IR(KBr): 1635 cm^{-1}.

mp: 154.0–157.0° C.

EXAMPLE 129

Synthesis of 1-(2-methoxybenzyl)-2-methyl-6-[(2-pyridylmethyl)carbamoyl]benzimidazole (194)

In the same manner as in Example 115, 0.918 g of 1-(2-methoxybenzyl)-2-methyl-6-[(2-pyridylmethyl) carbamoyl]benzimidazole (194) were formed from 0.997 g of 6-carboxy-1-(2-methoxybenzyl)-2-methylbenzimidazole, 0.858 g of oxalyl chloride, 0.309 g of 2-aminomethylpyridine and 1.02 g of triethylamine.

Properties of Compound (194):

^{1}H-NMR($CDCl_3$, δ): 2.60(3H, s), 3.89(3H, s), 4.77(2H, d, J=4.8 Hz), 5.36(2H, s), 6.60(1H, d, J=7.4 Hz), 6.79(1H, dt, J=0.8 and 7.4 Hz), 6.91(1H, d, J=7.4 Hz), 7.20–7.28(2H, m), 7.34(1H, d, J=7.9 Hz), 7.56(1H, br t), 7.66–7.75(3H, m), 7.95(1H, m), 8.57(1H, d, J=4.9 Hz).

IR(KBr): 1652 cm^{-1}.

mp: 136–138.5° C.

EXAMPLE 130

Synthesis of 1-(4-methoxybenzyl)-2-methyl-6-[(2-pyridylmethyl)carbamoyl]benzimidazole (195)

In the same manner as in Example 115, 0.697 g of 1-(4-methoxybenzyl)-2-methyl-6-[(2-pyridylmethyl) carbamoyl]benzimidazole (195) were formed from 0.985 g of 6-carboxy-1-(4-methoxybenzyl)-2-methylbenzimidazole, 0.858 g of oxalyl chloride, 0.309 g of 2-aminomethylpyridine and 1.02 g of triethylamine.

Properties of Compound (195):

^{1}H-NMR($CDCl_3$, δ): 2.59(3H, s), 3.76(3H, s), 4.78(2H, d, J=4.8 Hz), 5.32(2H, s), 6.83(2H, m), 7.00(2H, m), 7.22(1H, dd, J=5.1 and 6.8 Hz), 7.34(1H, d, J=7.8 Hz), 7.60(1H, br t), 7.67–7.76(3H, m), 7.97(1H, d, J=1.2 Hz), 8.57(1H, d, J=4.9 Hz).

IR(KBr): 1652 cm^{-1}.

mp: 191.5–192.2° C.

EXAMPLE 131

Synthesis of 1-[2-(benzenesulfonylmethyl)benzyl]-2-methyl-6-[(2-pyridylmethyl)carbamoyl] benzimidazole (196)

In the same manner as in Example 115, 0.64 g of 1-[2-(benzenesulfonylmethyl)benzyl]-2-methyl-6-[(2-pyridylmethyl)carbamoyl]benzimidazole (196) were formed from 0.74 g of 1-[2-(benzenesulfonylmethyl)benzyl]-6-carboxy-2-methylbenzimidazole, 0.45 g of oxalyl chloride, 0.19 g of 2-aminomethylpyridine and 0.53 g of triethylamine.

Properties of Compound (196):

^{1}H-NMR($CDCl_3$, δ): 2.57(3H, s), 4.50(2H, s), 4.74(2H, d, J=4.9 Hz), 5.59(2H, s), 6.63(1H, d, J=7.7 Hz), 6.87(1H, d, J=7.4 and 1.5 Hz), 7.09–7.19(3H, m), 7.31(1H, d, J=7.8 Hz), 7.53–7.61(3H, m), 7.64(1H, dt, J=7.6 and 1.6 Hz), 7.68–7.79 (5H, m), 7.84(1H, s), 8.52(1H, d, J=4.8 Hz).

IR(neat) 1646 cm^{-1}.

liquid.

EXAMPLE 132

Synthesis of 1-(2-cyanobenzyl)-2-methyl-6-[(2-pyridylmethyl)carbamoyl]benzimidazole (197)

In the same manner as in Example 115, 1.03 g of 1-(2-cyanobenzyl)-2-methyl-6-[(2-pyridylmethyl) carbamoyl]benzimidazole (197) were formed from 1.14 g of 6-carboxy-1-(2-cyanobenzyl)-2-methylbenzimidazole, 0.998 g of oxalyl chloride, 0.425 g of 2-aminomethylpyridine and 1.19 g of triethylamine.

Properties of Compound (197):

^{1}H-NMR($CDCl_3$, δ): 2.58(3H, s), 4.76(2H, d, J=4.8 Hz), 5.59(2H, s), 6.64(1H, d, J=7.4 Hz), 7.21(1H, dt, J=5.6 and 1.8 Hz), 7.33(1H, d, J=7.9 Hz), 7.39–7.47(2H, m), 7.65–7.79(5H, m), 7.89(1H, s), 8.56(1H, dd, J=4.9 and 0.9 Hz).

IR(KBr): 2223, 1642 cm^{-1}.

mp: 150.5–151.4° C.

EXAMPLE 133

Synthesis of 1-(biphenyl-2-ylmethyl)-2-methyl-6-[(2-pyridylmethyl)carbamoyl]benzimidazole (198)

In the same manner as in Example 115, 0.672 g of 1-(biphenyl-2-ylmethyl)-2-methyl-6-[(2-pyridylmethyl) carbamoyl]benzimidazole (198) were formed from 1.07 g of 1-(biphenyl-2-ylmethyl)-6-carboxy-2-methylbenzimidazole, 0.796 g of oxalyl chloride, 0.339 g of 2-aminomethylpyridine and 0.950 g of triethylamine.

Properties of Compound (198):

^{1}H-NMR($CDCl_3$, δ): 2.38(3H, s), 4.78(2H, d, J=4.8 Hz), 5.27(2H, s), 6.64(1H, d, J=8.0 Hz), 7.17–7.24(2H, m), 7.29–7.43(6H, m), 7.48(2H, t, J=5.5 Hz), 7.49(1H, s), 7.57–7.73(3H, m), 7.80(1H, d, J=1.0 Hz), 8.58(1H, d, J=4.9 Hz).

IR(KBr): 1630, 1619 cm^{-1}.

mp: 179.8–180.8° C.

EXAMPLE 134

Synthesis of 1-benzyl-2-methyl-6-[(2-pyridylmethyl)carbamoyl]benzimidazole (199)

In the same manner as in Example 115, 0.66 g of 1-benzyl-2-methyl-6-[(2-pyridylmethyl)carbamoyl] benzimidazole (199) were formed from 0.59 g of 1-benzyl-6-carboxy-2-methylbenzimidazole, 0.56 g of oxalyl chloride, 0.24 g of 2-aminomethylpyridine and 0.67 g of triethylamine.

Properties of Compound (199):

^{1}H-NMR($CDCl_3$, δ): 2.58(3H, s), 4.76(2H, d, J=4.9 Hz), 5.36(2H, s), 7.02–7.06(2H, m), 7.21(1H, dd, J=6.9 and 5.0 Hz), 7.27–7.35(4H, m), 7.65–7.75(4H, m), 7.96(1H, d, J=0.8 Hz), 8.56(1H, d, J=4.8 Hz).

IR(KBr): 1640 cm^{-1}.

mp: 124.0–124.9° C.

EXAMPLE 135

Synthesis of 1-(4-tert-butylbenzyl)-2-methyl-6-[(2-pyridylmethyl)carbamoyl]benzimidazole (200)

In the same manner as in Example 115, 0.477 g of 1-(4-tert-butylbenzyl)-2-methyl-6-[(2-pyridylmethyl) carbamoyl]benzimidazole (200) were formed from 0.544 g of 1-(4-tert-butylbenzyl)-6-carboxy-2-methylbenzimidazole, 0.428 g of oxalyl chloride, 0.183 g of 2-aminomethylpyridine and 0.511 g of triethylamine.

Properties of Compound (200):

^{1}H-NMR($CDCl_3$, δ): 1.27(9H, s), 2.60(3H, s), 4.77(2H, d, J=4.9 Hz), 5.34(2H, s), 6.98(2H, d, J=8.3 Hz), 7.21(1H, dd, J=7.3 and 5.1 Hz), 7.29–7.35(3H, m), 7.62(1H, br s), 7.65–7.75(3H, m), 7.96(1H, d, J=1.1 Hz), 8.57(1H, d, J=4.7 Hz).

IR(KBr): 1646 cm^{-1}.

mp: 140.4–142.8° C.

EXAMPLE 136

Synthesis of 2-methyl-1-(2-naphthylmethyl)-6-[(2-pyridylmethyl)carbamoyl]benzimidazole (201)

In the same manner as in Example 115, 0.47 g of 2-methyl-1-(2-naphthylmethyl)-6-[(2-pyridylmethyl) carbamoyl]benzimidazole (201) were formed from 0.80 g of 6-carboxy-2-methyl-1-(2-naphthylmethyl)benzimidazole, 0.64 g of oxalyl chloride, 0.27 g of 2-aminomethylpyridine and 0.77 g of triethylamine.

Properties of Compound (201):

^{1}H-NMR($CDCl_3$, δ): 2.60(3H, s), 4.75(2H, d, J=4.9 Hz), 5.52(2H, s), 7.17–7.23(2H, m), 7.31(1H, d, J=7.8 Hz), 7.38(1H, s), 7.43–7.48(2H, m), 7.60–7.82(7H, m), 8.00(1H, d, J=1.0 Hz), 8.53(1H, d, J=4.7 Hz).

IR(KBr): 1640 cm^{-1}.

mp: 143.0–144.5° C.

EXAMPLE 137

Synthesis of 1-(biphenyl-4-ylmethyl)-2-ethyl-6-[(2-pyridylmethyl)carbamoyl]benzimidazole (202)

In the same manner as in Example 115, 0.410 g of 1-(biphenyl-4-ylmethyl)-2-ethyl-6-[(2-pyridylmethyl) carbamoyl]benzimidazole (202) were formed from 0.500 g of 1-(biphenyl-4-ylmethyl)-6-carboxy-2-ethylbenzimidazole, 0.356 g of oxalyl chloride, 0.151 g of 2-aminomethylpyridine and 0.424 g of triethylamine.

Properties of Compound (202):

^{1}H-NMR($CDCl_3$, δ): 1.45(3H, t, J=7.7 Hz), 2.90(2H, q, J=7.4 Hz), 4.77(2H, d, J=4.7 Hz), 5.43(2H, s), 7.10(2H, d, J=8.2 Hz), 7.20(1H, dt, J=4.9 and 7.7 Hz), 7.33(2H, t, J=7.4 Hz), 7.42(2H, t, J=7.5 Hz), 7.49–7.55(4H, m), 7.61(1H, br t), 7.67(1H, dt, J=7.8 and 1.8 Hz), 7.72(1H, d, J=8.4 Hz), 7.81(1H, d, J=8.4 Hz), 7.99(1H, s), 8.56(1H, d, J=4.9 Hz).

IR(KBr): 1640 cm^{-1}.

mp: 123.0–124.0° C.

EXAMPLE 138

Synthesis of 1-(2-chlorobenzyl)-6-[2-(pyridylmethyl)carbamoyl]benzimidazole (203)

In the same manner as in Example 115, 0.110 g of 1-(2-chlorobenzyl)-6-[2-(pyridylmethyl)carbamoyl] benzimidazole (203) were formed from 0.461 g of 6-carboxy-1-(2-chlorobenzyl)benzimidazole, 0.728 g of oxalyl chloride, 0.174 g of 2-aminomethylpyridine and 0.486 g of triethylamine.

Properties of Compound (203):

^{1}H-NMR($CDCl_3$, δ): 4.78(2H, d, J=4.8 Hz), 5.51(2H, s), 6.92(1H, d, J=6.5 Hz), 7.17–7.31(3H, m), 7.34(1H, d, J=7.8

Hz), 7.45(1H, dd, J=1.1 and 8.0 Hz), 7.69(1H, dt, J=1.8 and 7.7 Hz), 7.67–7.73(1H, br s), 7.76(1H, dd, J=1.5 and 8.4 Hz), 7.87(1H, d, J=8.4 Hz), 8.05(2H, s), 8.57(1H, d, J=4.9 Hz).

IR(KBr): 1646 cm^{-1}.

mp: 144.0–145.0° C.

EXAMPLE 139

Synthesis of 2-methyl-1-(2-nitrobenzyl)-6-[(2-pyridylmethyl)carbamoyl]benzimidazole (204)

In the same manner as in Example 115, 0.241 g of 2-methyl-1-(2-nitrobenzyl)-6-[(2-pyridylmethyl) carbamoyl]benzimidazole (204) were formed from 0.367 g of 6-carboxy-2-methyl-1-(2-nitrobenzyl)benzimidazole, 0.299 g of oxalyl chloride, 0.217 g of 2-aminomethylpyridine and 0.360 g of triethylamine.

Properties of Compound (204):

^{1}H-NMR($CDCl_3$, δ): 2.56(3H, s), 4.75(2H, d, J=4.8 Hz), 5.83(2H, s), 6.41(1H, d, J=7.8 and 1.2 Hz), 7.22(1H, dt, J=5.0 and 1.7 Hz), 7.32(1H, d, J=7.9 Hz), 7.43–7.52(2H, m), 7.64(1H, s), 7.68(1H, dt, J=7.6 and 1.7 Hz),7.75(1H, dd, J=8.4 and 1.5 Hz), 7.80(1H, d, J=8.4 Hz), 7.82(1H, d, J=1.3 Hz), 8.28(1H, dd, J=8.0 and 1.7 Hz), 8.56(1H, d, J=4.9 Hz).

IR(KBr): 1645 cm^{-1}.

mp: 194.8–196.7° C.

EXAMPLE 140

Synthesis of 2-methyl-1-(2-nitrobenzyl)-5-[(2-pyridylmethyl)carbamoyl]benzimidazole (205)

In the same manner as in Example 115, 0.079 g of 2-methyl-1-(2-nitrobenzyl)-5-[(2-pyridylmethyl) carbamoyl]benzimidazole (205) were formed from 0.096 g of 5-carboxy-2-methyl-1-(2-nitrobenzyl)benzimidazole, 0.078 g of oxalyl chloride, 0.048 g of 2-aminomethylpyridine and 0.093 g of triethylamine.

Properties of Compound (205):

^{1}H-NMR($CDCl_3$, δ): 2.57(3H, s), 4.80(2H, d, J=4.7 Hz), 5.80(2H, s), 6.43(1H, d, J=7.4 and 0.8 Hz), 7.17(1H, d, J=8.4 Hz), 7.22(1H, dt, J=5.5 and 1.8 Hz), 7.35(1H, d, J=7.8 Hz), 7.44–7.52(2H, m), 7.67(1H, s), 7.69(1H, dt, J=7.8 and 1.9 Hz), 7.82(1H, dd, J=8.4 and 1.5 Hz), 8.27(1H, dd, J=8.0 and 1.6 Hz), 8.28(1H, d, J=1.4 Hz), 8.56(1H, d, J=4.9 Hz).

IR(KBr): 1645 cm^{-1}.

mp: ~96° C.(decomp.).

EXAMPLE 141

Synthesis of 1-(2-chlorobenzyl)-2-methyl-6-(2-naphthalenesulfonylcarbamoyl)benzimidazole sodium salt (206)

N,N'-carbonyldiimidazole (0.541 g) was added at a time to a solution of 0.500 g of 6-carboxy-1-(2-chlorobenzyl)-2-methylbenzimidazole in 20 ml of N,N-dimethylformamide, and the mixture was stirred at room temperature for 1 hour. Subsequently, a solution of 0.689 g of 2-naphthalenesulfonamide and 0.506 g of diazabicycloundecene in 5 ml of N,N-dimethylformamide were added thereto, and the mixture was stirred at 100° C. for 48 hours. The reaction solution was cooled, and the solvent was distilled off under reduced pressure. Water and chloroform were added to the residue, and 10% hydrochloric acid was added thereto until the aqueous layer was acidified. The mixture was extracted twice with chloroform. A saturated aqueous solution of sodium hydrogencarbonate was added to the resulting organic layer, and the mixed solution was stirred. The crystals precipitated were separated through filtration, and were dissolved in a small amount of methanol. Further, ethyl acetate was added thereto for crystallization. The crystals were separated through filtration, and were dried to give 0.508 g of 1-(2-chlorobenzyl)-2-methyl-6-(2-naphthalenesulfonylcarbamoyl)benzimidazole sodium salt (206).

Properties of Compound (206):

^{1}H-NMR(DMSO-d6, δ): 2.46(3H, s), 5.51(2H, s), 6.38 (1H, d, J=7.9 Hz), 7.17(1H, t, J=7.5 Hz), 7.30(1H, t), 7.45(1H, d, J=8.5 Hz), 7.51–7.57(3H, m), 7.77–7.93(5H, m), 7.99(1H, m), 8.35(1H, s).

IR(KBr): 1594 cm^{-1}.

Mass(FAB): m/e 512(M+1).

mp: 352.0–354.5° C.

EXAMPLE 142

Synthesis of 1-(2-chlorobenzyl)-2-methyl-6-(1-naphthalenesulfonylcarbamoyl)benzimidazole sodium salt (207)

In the same manner as in Example 141, 0.390 g of 1-(2-chlorobenzyl)-2-methyl-6-(1-naphthalenesulfonylcarbamoyl)benzimidazole sodium salt (207) were formed from 0.600 g of 6-carboxy-1-(2-chlorobenzyl)-2-methylbenzimidazole, 0.647 g of N,N'-carbonyldiimidazole, 0.829 g of 1-naphthalenesulfonamide and 0.608 g of diazabicycloundecene.

Properties of Compound (207):

^{1}H-NMR(DMSO-d6, δ): 2.46(3H, s), 5.49(2H, s), 6.39 (1H, d, J=7.8 Hz), 7.16(1H, t, J=7.5 Hz), 7.31(1H, t, J=7.3 Hz), 7.36(1H, t), 7.40–7.45(2H, m), 7.50(1H, t, J=7.7 Hz), 7.54(1H, d, J=8.0 Hz), 7.75–7.81(2H, m), 7.87(1H, d, J=7.9 Hz), 7.93(1H, d, J=8.2 Hz), 8.09(1H, d, J=7.3 Hz), 8.86(1H, d, J=8.5 Hz).

IR(KBr): 1633 cm^{-1}.

Mass(FAB): m/e 512(M+1).

mp: ~265° C.(decomp.).

EXAMPLE 143

Synthesis of 6-(4-chlorobenzenesulfonylcarbamoyl)-1-(2-chlorobenzyl)-2-methylbenzimidazole sodium salt (208)

In the same manner as in Example 141, 0.270 g of 6-(4-chlorobenzenesulfonylcarbamoyl)-1-(2-chlorobenzyl)-2-methylbenzimidazole sodium salt (208) were formed from 0.400 g of 6-carboxy-1-(2-chlorobenzyl)-2-methylbenzimidazole, 0.432 g of N,N'-carbonyldiimidazole, 0.510 g of 4-chlorobenzenesulfonamide and 0.404 g of diazabicycloundecene.

Properties of Compound (208):

^{1}H-NMR(DMSO-d6, δ): 2.46(3H, s), 5.52(2H, s), 6.38 (1H, d, J=7.4 Hz), 7.19(1H, t, J=7.6 Hz), 7.31(1H, t, J=7.6 Hz), 7.39(2H, d, J=8.5 Hz), 7.45(1H, d, J=8.9 Hz), 7.54(1H, d, J=8.0 Hz), 7.76–7.82(4H, m).

IR(KBr): 1592 cm^{-1}.

Mass(FAB): m/e 496(M+1).

mp: 360–362° C.(decomp.).

EXAMPLE 144

Synthesis of 6-(3-chlorobenzenesulfonylcarbamoyl)-1-(2-chlorobenzyl)-2-methylbenzimidazole (209)

In the same manner as in Example 141, 6-(3-chlorobenzenesulfonylcarbamoyl)-1-(2-chlorobenzyl)-2-

methylbenzimidazole sodium salt was obtained from 0.450 g of 6-carboxy-1-(2-chlorobenzyl)-2-methylbenzimidazole, 0.486 g of N,N'-carbonyldiimidazole, 0.573 g of 3-chlorobenzenesulfonamide and 0.456 g of diazabicycloundecene. This salt was dissolved in a mixed solution of methanol and water, and was adjusted to a pH of from 5 to 6 with 10% hydrochloric acid. The crystals precipitated were separated through filtration, and were dried to give 0.420 g of 6-(3-chlorobenzenesulfonylcarbamoyl)-1-(2-chlorobenzyl)-2-methylbenzimidazole (209).

Properties of Compound (209):

^{1}H-NMR(DMSO-d6, δ): 2.51(3H, s), 5.63(2H, s), 6.48 (1H, d, J=7.7 Hz), 7.22(1H, t, J=7.6 Hz), 7.34(1H, t, J=7.7 Hz), 7.56(1H, t, J=8.0 Hz), 7.64(1H, t, J=8.0 Hz), 7.68(1H, d, J=8.5 Hz), 7.78(2H, t, J=8.6 Hz), 7.91(1H, d, J=7.6 Hz), 7.95(1H, d, J=1.6 Hz), 8.10(1H, s).

IR(KBr): 1687 cm^{-1}.

Mass(FAB): m/e 474(M+1).

mp: 254.5–257.5° C.(decomp.).

EXAMPLE 145

Synthesis of 5-benzenesulfonylcarbamoyl-2-benzyl-1-(2-chlorobenzyl)benzimidazole (210)

In the same manner as in Example 144, 0.447 g of 5-benzenesulfonylcarbamoyl-2-benzyl-1-(2-chlorobenzyl) benzimidazole (210) were formed from 0.466 g of 2-benzyl-5-carboxy-1-(2-chlorobenzyl)benzimidazole, 0.401 g of N,N'-carbonyldiimidazole, 0.389 g of benzenesulfonamide and 0.377 g of diazabicycloundecene.

Properties of Compound (210):

^{1}H-NMR(DMSO-d6, δ): 4.28(2H, s), 5.57(2H, s), 6.23 (1H, d, J=7.6 Hz), 7.04(1H, t, J=7.6 Hz), 7.10–7.26(6H, m), 7.40(1H, d, J=8.6 Hz), 7.46(1H, d, J=8.0 Hz), 7.61–7.73(4H, m), 8.00(2H, d, J=7.6 Hz), 8.23(1H, s), 12.43(1H, br s).

IR(KBr): 1685 cm^{-1}.

mp: 152.0–155.0° C.

EXAMPLE 146

Synthesis of 6-benzenesulfonylcarbamoyl-2-benzyl-1-(2-chlorobenzyl)benzimidazole (211)

In the same manner as in Example 144, 0.803 g of 6-benzenesulfonylcarbamoyl-2-benzyl-1-(2 -chlorobenzyl) benzimidazole (211) were formed from 0.760 g of 2-benzyl-6-carboxy-1-(2-chlorobenzyl)benzimidazole, 0.654 g of N,N'-carbonyldiimidazole, 0.634 g of benzenesulfonamide and 0.614 g of diazabicycloundecene.

Properties of Compound (211):

^{1}H-NMR(DMSO-d6, δ): 4.41(2H, s), 5.71(2H, s), 6.32 (1H, d, J=7.7 Hz), 7.06(1H, t, J=7.7 Hz), 7.14–7.30(6H, m), 7.50(1H, d, J=8.0 Hz), 7.62(2H, t), 7.70(1H, t), 7.81(1H, d, J=8.6 Hz), 7.87(1H, d, J=8.5 Hz), 7.97(2H, d, J=8.2 Hz), 8.16(1H, s), 12.60(1H, br s).

IR(KBr): 1704 cm^{-1}.

mp: 143.0–144.5° C.

EXAMPLE 147

Synthesis of 1-(2,4-dichlorobenzyl)-2-methyl-6-[(2-pyridylmethyl)carbamoyl]benzimidazole (180)

Ten milliliters of dichloromethane and 1 drop of N,N-dimethylformamide were added to 0.627 g of 6-carboxy-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole, and the mixture was cooled with ice. Oxalyl chloride (0.493 g) was added dropwise thereto, and the mixture was stirred for several minutes. Further, the mixture was stirred at room temperature for 1 hour, and was then concentrated under reduced pressure to remove oxalyl chloride. The residue was dissolved in 10 ml of dichloromethane. This solution was added dropwise to a solution of 0.167 g of 2-aminomethylpyridine and 0.469 g of triethylamine in 5 ml of methylene chloride while being cooled with ice. After the mixture was stirred for 1 hour, the reaction solution was washed three times with water and further with a saturated aqueous solution of sodium hydrogencarbonate. The organic layer was concentrated under reduced pressure, and was purified through preparative thin-layer silica-gel chromatography (eluent: a mixture of acetone and diethyl ether at a ratio of 1:1). The resulting product was further dissolved in 5 ml of ethyl acetate, and 2 ml of hexane were added thereto for crystallization. The crystals were separated through filtration, and were dried to give 0.359 g of 1-(2,4-dichlorobenzyl)-2-methyl-6-[(2-pyridylmethyl)carbamoyl] benzimidazole (180).

Properties of Compound (180):

^{1}H-NMR($CDCl_3$, δ): 2.56(3H, s), 4.76(2H, d, J=4.8 Hz), 5.40(2H, s), 6.33(1H, d, J=8.4 Hz), 7.07(1H, dd, J=8.4 and 2.0 Hz), 7.22(1H, dd, J=7.4 and 4.9 Hz), 7.33(1H, d, J=7.9 Hz), 7.48(1H, d, J=2.1 Hz), 7.62–7.79(4H, m), 7.86(1H, d, J=1.1 Hz), 8.57, (1H, d, J=4.9 Hz).

IR(KBr): 1645 cm^{-1}.

mp: 204.1–206.3° C.

EXAMPLE 148

Synthesis of 1-(biphenyl-4-ylmethyl)-2-methyl-6-[(2-pyridylmethyl)carbamoyl]benzimidazole (212)

Oxalyl chloride (0.655 g) was added to a solution of 0.886 g of 1-(biphenyl-4-ylmethyl)-6-carboxy-2-methylbenzimidazole and 1 drop of N,N-dimethylformamide in 13 ml of dichloromethane while being cooled with ice, and the mixture was stirred at room temperature for 15 hours. The crystals precipitated were separated through filtration, washed with methylene chloride, and dried under reduced pressure. The crystals were added to a solution of 0.235 g of 2-aminomethylpyridine and 0.653 g of triethylamine in 15 ml of dichloromethane while being cooled, and the mixture was stirred for 1 hour. Water was added to the reaction solution to stop the reaction. The reaction solution was washed twice with water and further with a saturated aqueous solution of sodium hydrogencarbonate. The organic layer was then dried, and the solvent was concentrated under reduced pressure. The residue was recrystallized from a mixed solvent of ethyl acetate and ethanol to give 0.774 g of 1-(biphenyl-4-ylmethyl)-2-methyl-6-[(2-pyridylmethyl) carbamoyl]benzimidazole (212).

Properties of Compound (212):

^{1}H-NMR($CDCl_3$, δ): 2.62(3H, s), 4.77(2H, d, J=4.8 Hz), 5.42(2H, s), 7.12(2H, d, J=8.5 Hz), 7.21(1H, m), 7.34(2H, m), 7.42(2H, m), 7.51–7.55(4H, m),7.62(1H, br t), 7.67(1H, dt, J=1.7 and 7.7 Hz), 7.71(1H, dd, J=1.6 and 8.4 Hz), 7.76(1H, d, J=8.4 Hz), 8.00(1H, d, J=1.2 Hz), 8.56(1H, d, J=4.8 Hz).

IR(KBr): 1642 cm^{-1}.

mp: 205.0–206.5° C.

EXAMPLE 149

Synthesis of 6-benzenesulfonylcarbamoyl-1-(2-chlorobenzyl)-2-methylbenzimidazole (163)

N,N'-carbonyldiimidazole (0.973 g) was added to a solution of 0.902 g of 6-carboxy-1-(2-chlorobenzyl)-2-

methylbenzimidazole in 20 ml of N,N-dimethylformamide, and the mixture was stirred at room temperature for 1 hour. Subsequently, a solution of 0.943 g of benzenesulfonamide and 0.913 g of diazabicycloundecene in 5 ml of N,N-dimethylformamide was added thereto, and the mixture was stirred at 100° C. for 70 hours. The reaction solution was cooled, and the solvent was distilled off under reduced pressure. Water and chloroform were added to the residue, and 10% hydrochloric acid was added thereto while being stirred until the aqueous layer was acidified. The mixed solution was extracted twice with chloroform. The resulting organic layer was washed with a saturated aqueous solution of sodium hydrogencarbonate, and the solvent was distilled off under reduced pressure. The residue was dissolved in a small amount of chloroform, and ethyl acetate was added to the solution for crystallization. The crystals were separated through filtration, and were dried to give 0.667 g of 6-benzenesulfonylcarbamoyl-1-(2-chlorobenzyl)-2-methylbenzimidazole (163).

EXAMPLE 150

Synthesis of 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-methylbenzimidazole sodium salt (213)

In the same manner as in Example 141, 0.365 g of 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-methylbenzimidazole sodium salt (213) were formed from 0.637 g of 6-carboxy-1-(biphenyl-4-ylmethyl)-2-methylbenzimidazole, 0.533 g of N,N'-carbonyldiimidazole, 0.516 g of benzenesulfonamide and 0.500 g of diazabicycloundecene.

Properties of Compound (213):

^{1}H-NMR(DMSO-d6, δ): 2.52(3H, s), 5.52(2H, S), 7.13 (2H, d, J=8.1 Hz), 7.31–7.37(4H, m), 7.39–7.45(3H, m), 7.58–7.63(4H, m), 7.78–7.82(3H, m), 7.97(1H, s).

IR(Nujol): 1591 cm^{-1}.

mp: 289.0–290.0° C.(decomp.).

EXAMPLE 151

Synthesis of 6-benzenesulfonylcarbamoyl-1-(2-chlorobenzyl)-2-methylbenzimidazole (163)

N,N'-carbonyldiimidazole (5.41 g) was added at a time to a solution of 5.02 g of 6-carboxy-1-(2-chlorobenzyl)-2-methylbenzimidazole in 110 ml of N,N-dimethylformamide, and the mixture was stirred at room temperature for 1 hour. Subsequently, a solution of 5.24 g of benzenesulfonamide and 5.08 g of diazabicycloundecene in 20 ml of N,N-dimethylformamide was added thereto, and the mixed solution was stirred at 100° C. for 70 hours. The reaction solution was cooled, and the solvent was distilled off under reduced pressure. Water and chloroform were added to the residue, and 10% hydrochloric acid was added thereto while being stirred until the aqueous layer was acidified. The solution was extracted twice with chloroform. The organic layer was washed with a saturated aqueous solution of sodium hydrogencarbonate, and a part of the solvent was distilled off under reduced pressure. The crystals precipitated were separated through filtration, and were dried to give 4.96 g of 6-benzenesulfonylcarbamoyl-1-(2-chlorobenzyl)-2-methylbenzimidazole (163).

EXAMPLE 152

Synthesis of 1-(2-chlorobenzyl)-2-methyl-6-trifluoromethanesulfonylcarbamoylbenzimidazole hydrochloride (214)

N,N'-carbonyldiimidazole (0.647 g) was added at a time to a solution of 0.600 g of 6-carboxy-1-(2-chlorobenzyl)-2-methylbenzimidazole in 20 ml of N,N-dimethylformamide, and the mixture was stirred at room temperature for 1 hour. Subsequently, a solution of 0.596 g of trifluoromethanesulfonamide and 0.609 g of diazabicycloundecene in 5 ml of N,N-dimethylformamide was added thereto, and the mixture was stirred at 100° C. for 72 hours. The reaction solution was cooled, and the solvent was distilled off under reduced pressure. Water and ethyl acetate were added to the residue, and 10% hydrochloric acid was added thereto while being stirred until the aqueous layer was acidified. The crystals precipitated were washed with a mixed solvent of 25 ml of ethanol and 25 ml of methanol. The crystals were dried to give 0.420 g of 1-(2-chlorobenzyl)-2-methyl-6-trifluoromethanesulfonylcarbamoylbenzimidazole hydrochloride (214).

Properties of Compound (214):

^{1}H-NMR(DMSO-d6, δ): 2.84(3H, s), 5.82(2H, s), 7.08 (1H, d, J=7.5 Hz), 7.30(1H, t), 7.40(1H, t, J=7.7 Hz), 7.58(1H, d, J=8.0 Hz), 7.79(1H, d, J=8.6 Hz), 8.07–8.13(2H, m).

IR(KBr): 1634 cm^{-1}.

Mass(CI): m/e 432(M+1-HCl).

mp: 332–335° C.(decomp.).

EXAMPLE 153 AND 154

Synthesis of 6-benzenesulfonylcarbamoyl-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole hydrochloride (215) and 6-benzenesulfonylcarbamoyl-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole (216)

In the same manner as in Example 152, 0.540 g of 6-benzenesulfonylcarbamoyl-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole hydrochloride (215) were formed from 0.460 g of 6-carboxy-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole, 0.455 g of N,N'-carbonyldiimidazole, 0.431 g of benzenesulfonamide and 0.418 g of diazabicycloundecene.

Properties of Compound (215):

^{1}H-NMR(DMSO-d6, δ): 2.71(3H, s), 5.74(2H, s), 6.83 (1H, d, J=8.4 Hz), 7.33(1H, dd, J=2.0 and 8.4 Hz), 7.63(2H, t), 7.71(1H, t), 7.78(1H, d, J=2.0 Hz), 7.86(1H, d, J=8.7 Hz), 7.95(1H, dd, J=1.4 and 8.7 Hz), 7.99(2H, m), 8.29(1H, s).

IR(KBr): 1686 cm^{-1}.

mp: 236.0–238.0° C.

This compound was dissolved in a mixed solvent of a potassium hydrogencarbonate and methanol, and the solution was adjusted to a pH of from 5 to 6 with 10% hydrochloric acid. The crystals precipitated were collected, washed with water and with methanol, and dried to give 6-benzenesulfonylcarbamoyl-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole (216).

Properties of Compound (216):

^{1}H-NMR(DMSO-d6, δ): 2.48(3H, s), 5.58(2H, s), 6.42 (1H, d, J=8.4 Hz), 7.31(1H, dd, J=2.2 and 8.4 Hz), 7.60–7.75 (6H, m), 7.99(2H, d, J=7.4 Hz), 8.06(1H, s), 12.40(1H, s).

IR(KBr): 1540 cm^{-1}.

mp: 238.2.–239.9° C.

EXAMPLE 155

Synthesis of 1-(2-chlorobenzyl)-6-(4-methoxybenzenesulfonylcarbamoyl)-2-methylbenzimidazole (217)

N,N'-carbodiimidazole (0.431 g) was added at a time to a solution of 0.400 g of 6-carboxy-1-(2-chlorobenzyl)-2-

methylbenzimidazole in 15 ml of N,N-dimethylformamide, and the mixture was stirred at room temperature for 1 hour. Subsequently, a solution of 0.498 g of 4-methoxybenzenesulfonamide and 0.405 g of diazabicycloundecene in 5 ml of N,N-dimethylformamide was added thereto, and the mixed solution was stirred at 100° C. for 67 hours. The reaction solution was cooled, and the solvent was distilled off under reduced pressure. Water and chloroform were added to the residue, and 10% hydrochloric acid was added thereto while being cooled until the aqueous layer was acidified. The resulting mixture was extracted twice with chloroform. The organic layer was washed with a saturated aqueous solution of sodium hydrogencarbonate, and the solvent was distilled off under reduced pressure. The residue was purified through silica-gel column chromatography (eluent: a mixture of chloroform and methanol at a ratio of 100:2 to 100:10). The resulting product was concentrated, and was crystallized from a mixed solution of ethyl acetate and diethyl ether. The crystals were separated through filtration, and were dried to give 0.450 g of 1-(2-chlorobenzyl)-6-(4-methoxybenzenesulfonylcarbamoyl)-2-methylbenzimidazole (217).

Properties of Compound (217):

^{1}H-NMR(DMSO-d6, δ): 2.46(3H, s), 3.83(3H, s), 5.58 (2H, s), 7.12(2H, d, J=9.0 Hz), 7.21(1H, t, J=7.3 Hz), 7.33(1H, t), 7.56(1H, d, J=7.0 Hz), 7.63(1H, d, J=8.5 Hz), 7.71(1H, dd, J=1.6 and 8.5 Hz), 7.91(2H, d, J=9.0 Hz), 8.05(1H, d, J=1.3 Hz).

IR(KBr): 1683 cm^{-1}.

Mass(FAB): m/e 470(M+1).

mp: 271.0–274.0° C.

EXAMPLE 156

Synthesis of 1-(2-chlorobenzyl)-2-methyl-6-(α-toluenesulfonylcarbamoyl)benzimidazole (218)

In the same manner as in Example 155, 0.350 g of 1-(2-chlorobenzyl)-2-methyl-6-(α-toluenesulfonylcarbamoyl)benzimidazole (218) were formed from 0.450 g of 6-carboxy-1-(2-chlorobenzyl)-2-methylbenzimidazole, 0.485 g of N,N-carbonyldiimidazole, 0.512 g of a-toluenesulfonamide and 0.456 g of diazabicycloundecene.

Properties of Compound (218):

^{1}H-NMR(DMSO-d6, δ): 2.48(3H, s), 4.36(2H, s), 5.53 (2H, s), 6.40(1H, d, J=6.8 Hz), 7.15–7.28(6H, m), 7.32(1H, t), 7.49(1H, d, J=8.3 Hz), 7.55(1H, d), 7.83–7.87(2H, m).

IR(KBr): 1593 cm^{-1}.

Mass(FAB): m/e 454(M+1).

mp: 193–196° C.(foamed)

EXAMPLE 157

Synthesis of 1-(2-chlorobenzyl)-6-(2,5-dimethylbenzenesulfonylcarbamoyl)-2-methylbenzimidazole (219)

In the same manner as in Example 155, 0.490 g of 1-(2-chlorobenzyl)-6-(2,5-dimethylbenzenesulfonylcarbamoyl)-2-methylbenzimidazole (219) were formed from 0.500 g of 6-carboxy-1-(2-chlorobenzyl)-2-methylbenzimidazole, 0.539 g of N,N'-carbonyldiimidazole, 0.616 g of 2,5-xylenesulfonamide and 0.506 g of diazabicycloundecene.

Properties of Compound (219):

^{1}H-NMR(DMSO-d6, δ): 2.35(3H, s), 2.48(3H, s), 2.51 (3H, s), 5.58(2H, s), 6.45(1H, d, J=7.5 Hz), 7.20–7.27(2H, m), 7.31–7.39(2H, m), 7.56(1H, d, J=8.0 Hz), 7.64(1H, d, J=8.5 Hz), 7.75(1H, d, J=8.5 Hz), 7.82(1H, s), 8.06(1H, s), 12.45(1H, br s).

IR(KBr): 1690 cm^{-1}.

Mass(FAB): m/e 468(M+1).

mp: 266.5–267.5° C.

EXAMPLE 158

Synthesis of 1-(2-chlorobenzyl)-2-methyl-6-(4-nitrobenzenesulfonylcarbamoyl)benzimidazole (220)

N,N'-carbodiimidazole (0.432 g) was added at a time to a solution of 0.400 g of 6-carboxy-1-(2-chlorobenzyl)-2-methylbenzimidazole in 15 ml of N,N-dimethylformamide, and the solution was stirred at room temperature for 1 hour. Subsequently, a solution of 0.538 g of 4-nitrobenzenesulfonamide and 0.405 g of diazabicycloundecene in 5 ml of N,N-dimethylformamide, and the mixture was stirred at 100° C. for 84 hours. The reaction solution was cooled, and the solvent was distilled off under reduced pressure. Chloroform and hydrochloric acid were added to the residue, and the mixture was stirred to precipitate the crystals. The crystals precipitated were separated through filtration, and were dried to give 0.300 g of 1-(2-chlorobenzyl)-2-methyl-6-(4-nitrobenzenesulfonylcarbamoyl)benzimidazole (220).

Properties of Compound (220):

^{1}H-NMR(DMSO-d6, δ): 2.56(3H, s), 5.65(2H, s), 6.54 (1H, d, J=7.6 Hz), 7.23(1H, t, J=7.6 Hz), 7.34(1H, t, J=7.6 Hz), 7.56(1H, t, J=8.0 Hz), 7.68(1H, d, J=8.5 Hz), 7.83(1H, d, J=8.3 Hz), 8.07(1H, s), 8.16(2H,d,J=8.7 Hz), 8.37(2H, d, J=8.7 Hz).

IR(KBr): 1621 cm^{-1}.

Mass(FAB): m/e 485(M+1).

mp: 330–332° C.

EXAMPLE 159

Synthesis of 1-(2-chlorobenzyl)-2-methyl-6-[4-(trifluoromethyl)benzenesulfonylcarbamoyl] benzimidazole (221)

In the same manner as in Example 158, 0.390 g of 1-(2-chlorobenzyl)-2-methyl-6-[4-(trifluoromethyl) benzenesulfonylcarbamoyl]benzimidazole (221) were formed from 0.450 g of 6-carboxy-1-(2-chlorobenzyl)-2-methylbenzimidazole, 0.486 g of N,N'-carbonyldiimidazole, 0.676 g of 4-(trifluoromethyl)benzenesulfonamide and 0.457 g of diazabicycloundecene.

Properties of Compound (221):

^{1}H-NMR(DMSO-d6, δ): 2.52(3H, s), 5.62(2H, s), 6.47 (1H, d, J=7.2 Hz), 7.22(1H, t, J=7.5 Hz), 7.34(1H, t), 7.56(1H, d, H=8.0 Hz), 7.66(1H, d, 8.5 Hz), 7.78(1H, d), 7.97(2H, d, J=8.3 Hz), 8.06(1H, s), 8.15(2H, d, J=8.3 Hz).

IR(KBr): 1620 cm^{-1}.

Mass(FAB): m/e 508(M+1).

mp: 288.0–292.0° C.

EXAMPLE 160

Synthesis of 6-(2-chlorobenzenesulfonylcarbamoyl)-1-(2-chlorobenzyl)-2-methylbenzimidazole ammonium salt (222)

N,N'-carbodiimidazole (0.485 g) was added at a time to a solution of 0.450 g of 6-carboxy-1-(2-chlorobenzyl)-2-

methylbenzimidazole in 15 ml of N,N-dimethylformamide and the mixture was stirred at room temperature for 1 hour. Subsequently, a solution of 0.575 g of trifluoromethanesulfonamide and 0.457 g of diazabicycloundecene in 5 ml of N,N-dimethylformamide was added thereto, and the mixture was stirred at 100° C. for 72 hours. The reaction solution was cooled, and the solvent was distilled off under reduced pressure. Water and ethyl acetate were added to the residue, and 10% hydrochloric acid was added thereto while being mixed until the aqueous layer was acidified. The crystals precipitated were separated through filtration. The crystals were dissolved in ethanol, and the solution was adjusted to a pH of 7 with aqueous ammonia. Further, diisopropyl ether was added thereto. The crystals precipitated were separated through filtration, and were dried to give 0.360 g of 6-(2-chlorobenzenesulfonylcarbamoyl)-1-(2-chlorobenzyl)-2-methylbenzimidazole ammonium salt (222).

Properties of Compound (222):

^{1}H-NMR(DMSO-d6, δ): 2.47(3H, s), 5.51(2H, s), 6.43 (1H, d, J=7.5 Hz), 7.12(4H, br s), 7.19(1H, t, J=7.6 Hz), 7.28–7.38(4H, m), 7.46(1H, d, J=8.3 Hz), 7.53(1H, d, J=7.9 Hz), 7.78–7.82(2H, m), 7.97(1H, m).

IR(KBr): 1590 cm^{-1}.

Mass(FAB): m/e 474(M+1-NH3).

mp: 264.0–267.0° C.

EXAMPLE 161

Synthesis of 6-carbamoyl-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole (223)

Oxalyl chloride (0.437 g) was added to a solution of 0.490 g of 6-carboxy-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole and 1 drop of N,N-dimethylformamide in 8 ml of methylene chloride while being cooled with ice, and the mixture was stirred at room temperature for 1.5 hours. Four milliliters of 28% aqueous ammonia were added thereto, and the solution was stirred at room temperature for 12 hours. The reaction solution was extracted with the addition of water and methylene chloride. The organic layer was concentrated, and the crystals precipitated were then collected, and were dried to give 0.240 g of 6-carbamoyl-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole (223).

Properties of Compound (223):

^{1}H-NMR(DMSO-d6, δ): 2.48(3H, s), 5.54(2H, s), 6.41 (1H, d, J=8.4 Hz), 7.21–8.02(3H, m), 7.31(1H, dd, J=2.2 and 8.4 Hz), 7.60(1H, d, J=8.4 Hz), 7.75(1H, m), 7.93(1H, s).

IR(KBr): 1666 cm^{-1}.

mp: 112.0–114.0° C.

EXAMPLE 162

Synthesis of 6-benzensulfonylcarbamoyl-2-benzyl-1-(2,4-dichlorobenzyl)benzimidazole (224)

N,N'-carbonyldiimidazole (0.248 g) was added at a time to a solution of 0.315 g of 2-benzyl-6-carboxy-1-(2,4-dichlorobenzyl)benzimidazole in 5 ml of N,N-dimethylformamide, and the mixture was stirred at room temperature for 1 hour. Subsequently, a solution of 0.240 g of benzenesulfonamide and 0.233 g of diazabicycloundecene in 4 ml of N,N-dimethylformamide was added thereto, and the mixture was stirred at 100° C. for 62 hours. The reaction solution was cooled, and the solvent was distilled off under reduced pressure. Water and chloroform were added to the residue, and 10% hydrochloric acid was added thereto while being mixed until the aqueous layer was acidified. The solution was extracted twice with chloroform. The resulting organic layer was washed with a saturated aqueous solution of sodium hydrogencarbonate, and a part of the solvent was distilled off under reduced pressure. To the residue were added 4 ml of methanol and 4 ml of a 20% potassium hydrogencarbonate aqueous solution to form a uniform solution. This solution was then adjusted to a pH of from 5 to 6 with 10% hydrochloric acid. The crystals precipitated were separated through filtration, and were dried to give 0.310 g of 6-benzenesulfonylcarbamoyl-2-benzyl-1-(2,4-dichlorobenzyl)benzimidazole (244).

Properties of Compound (224):

^{1}H-NMR(DMSO-d6, δ): 4.32(1H, s), 5.61(2H, s), 6.16 (1H, d, J=8.4 Hz), 7.09(1H, dd, J=8.4 and 1.9 Hz), 7.18–7.10 (5H, m), 7.82–7.58(6H, m), 7.97(2H, d, J=7.6 Hz), 8.10(1H, s), 12.43(1H, br s).

IR(KBr): 1703 cm^{-1}.

mp: 236.0–238.0° C.

EXAMPLE 163

Synthesis of 5-benzenesulfonylcarbamoyl-2-benzyl-1-(2,4-dichlorobenzyl)benzimidazole (225)

In the same manner as in Example 152, 0.270 g of 5-benzenesulfonylcarbamoyl-2-benzyl-1-(2,4-dichlorobenzyl)benzimidazole (225) were formed from 0.385 g of 2-benzyl-5-carboxy-1-(2,4-dichlorobenzyl) benzimidazole, 0.304 g of N,N'-carbonyldiimidazole, 0.294 g of benzenesulfonamide and 0.285 g of diazabicycloundecene.

Properties of Compound (225):

^{1}H-NMR(DMSO-d6, δ): 4.28(2H, s), 5.52(2H, s), 6.14 (1H, d, J=8.4 Hz), 7.21–7.06(6H, m), 7.42(1H, d, J=8.6 Hz), 7.76–7.57(5H, m), 8.05–7.95(2H, m), 8.24(1H, s), 12.43 (1H, br s).

IR(KBr): 1691 cm^{-1}.

mp: 107.0–110.0° C.

EXAMPLE 164

Synthesis of 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl-2-hydroxybenzimidazole (226)

Tetramethoxymethane (0.220 g) was added to a solution of 0.400 g of N-benzenesulfonyl-4-amino-3-(biphenyl-4-ylmethylamino)benzamide in 5 ml of acetic acid, and the mixture was stirred at 80° C. for 2 hours. The reaction solution was concentrated, and a 20% potassium hydrogencarbonate aqueous solution was added to this reaction solution to render it basic. This solution was then adjusted to a pH of from 5 to 6 with 10% hydrochloric acid. The crystals precipitated were collected, and 10 ml of methanol, 0.50 g of 10% hydrochloric acid and 0.35% hydrochloric acid were added thereto. The mixture was stirred at 60° C. for 15 hours. A 20% potassium hydrogencarbonate aqueous solution was added to the solution to render it alkaline. This solution was then adjusted to a pH of from 5 to 6 with 10% hydrochloric acid. The crystals precipitated were separated through filtration, and were dried to give 0.219 g of 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl-2-hydroxybenzimidazole (226).

Properties of Compound (226):

^{1}H-NMR(DMSO-d6, δ): 5.07(2H, s), 7.08(1H, d, J=8.2 Hz), 7.33–7.39(3H, m), 7.44(2H, t, J=7.5 Hz), 7.60–7.65 (7H, m), 7.66–7.72(2H, m), 7.96–7.80(2H, m), 11.46(1H, s), 12.34(1H, s).

IR(KBr): 1704, 1686 cm^{-1}.

Mass(FD): m/e 483(M).

mp: 268.7–273.9° C.

EXAMPLE 165

Synthesis of 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-mercaptobenzimidazole (227)

Two milliliters of carbon disulfide were added to a solution of 0.800 g of N-benzenesulfonylcarbamoyl-4-amino-3-(biphenyl-4-ylmethylamino)benzamide, and the mixture was stirred at 50° C. for 70 hours. Chloroform and water were added thereto. The crystals precipitated were separated through filtration, and were dried to give 0.719 g of 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-mercaptobenzimidazole (227).

Properties of Compound (227):

^{1}H-NMR(DMSO-d6, δ): 5.55(2H, s), 7.28(1H, d, J=8.4 Hz), 7.35(1H, t, J=6.3 Hz), 7.39–7.47(4H, m), 7.61–7.65 (6H, m), 7.69(1H, t, J=7.4 Hz), 7.78(1H, dd, J=8.4 and 1.4 Hz), 7.87(1H, s), 7.81–7.98(2H, m), 12.51(1H, s), 13.29(1H, s).

IR(KBr): 1701 cm^{-1}.

mp: 320.0–321.0° C.

EXAMPLE 166

Synthesis of 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-methoxybenzimidazole (228)

Tetramethoxymethane (0.250 g) was added to a solution of 0.400 g of N-benzenesulfonyl-4-amino-3-(biphenyl-4-ylmethylamino)benzamide in 3 ml of acetic acid, and the mixture was stirred at 80° C. for 2 hours. Methanol was added to the reaction solution, and the crystals precipitated were collected. The crystals were washed with a mixed solvent of 1 ml of acetone and 8 ml of methanol, separated through filtration, and dried to give 0.280 g of 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-methoxybenzimidazole (228).

Properties of Compound (228):

^{1}H-NMR(DMSO-d6, δ): 4.17(3H, s), 5.33(2H, s), 7.30 (2H, d, J=8.2 Hz), 7.35(1H, t, J=7.4 Hz), 7.44(2H, t, J=7.5 Hz), 7.50(1H, d, J=8.4 Hz), 7.60–7.65(6H, m), 7.68–7.72 (2H, m), 7.98–8.01(2H, m), 8.05(1H, d, J=1.5 Hz), 8.18(1H, s), 12.50(1H, s).

IR(KBr): 1690 cm^{-1}.

mp: 136.0–138.5° C.

EXAMPLE 167

Synthesis of 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-carboxybenzimidazole (229)

Triethylamine (0.080 g) and 0.148 g of methyloxalyl chloride were added to a solution of 0.400 g of N-benzenesulfonyl-4-amino-3-(biphenyl-4-ylmethylamino) benzamide in 3 ml of N,N-dimethylformamide, and the mixture was stirred at room temperature for 2 hours. The reaction solution was concentrated, and the residue was purified through silica-gel column chromatography (eluent: a mixture of ethyl acetate and methanol at a ratio of 9:1) to obtain crude 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-carboxybenzimidazole. This compound was dissolved in 1 ml of acetic acid and 5 ml of methanol, and the mixture was stirred at 60° C. for 15 hours. The reaction solution was neutralized with a potassium hydroxide aqueous solution. The crystals precipitated were separated through filtration, and were dried to give 0.245 g of 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-carboxybenzimidazole (229).

Properties of Compound (229):

^{1}H-NMR(DMSO-d6, δ): 5.44(2H, s), 7.23(1H, d, J=8.4 Hz), 7.36(1H, t, J=7.6 Hz), 7.41(2H, d, J=8.1 Hz), 7.45(2H, t, J=7.5 Hz), 7.58(2H, t, J=7.8 Hz), 7.60–7.71(7H, m), 7.94(2H, d, J=8.3 Hz), 12.38(1H, s), 12.52(1H, s).

IR(KBr): 1670 cm^{-1}.

mp: 247.5–250.0° C.

EXAMPLE 168

Synthesis of 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-methylaminobenzimidazole (230)

A mixture containing 0.300 g of N-benzenesulfonylcarbamoyl-4-amino-3-(biphenyl-4-ylmethylamino)benzamide, 0.200 g of methyl isothiocyanate, 5 ml of methanol and 5 ml of acetone was stirred at room temperature for 12 hours. Further, 1 ml of 97% sulfuric acid was added thereto, and the mixture was stirred at room temperature for 43 hours. A 20% potassium hydrogencarbonate aqueous solution was added to the reaction solution to render it basic. This reaction solution was then concentrated, and the residue was extracted with ethyl acetate and with water. The organic layer was concentrated, dissolved in chloroform, and precipitated with hexane. The crystals precipitated were separated through filtration, and were dried to give 0.140 g of 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-methylaminobenzimidazole (230).

Properties of Compound (230):

^{1}H-NMR(DMSO-d6, δ): 2.98(3H, d, J=4.4 Hz), 5.34(2H, s), 7.22(2H, d, J=8.2 Hz), 7.26(1H, d, J=8.4 Hz), 7.34(1H, t, J=7.3 Hz), 7.44(2H, t, J=7.5 Hz), 7.57(2H, t, J=7.6 Hz), 7.59–7.68(6H, m), 7.76(1H, s), 7.95(2H, d, J=7.4 Hz), 12.28(1H, s).

IR(KBr): 1672 cm^{-1}.

Mass(FAB): m/e 497(M+1).

mp: 225.0–228.0° C.

EXAMPLE 169

Synthesis of 2-amino-6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)benzimidazole (231)

Ten milliliters of methanol, 10 ml of acetone and 0.395 g of cyanogen bromide were added to 1.500 g of N-benzenesulfonylcarbamoyl-4-amino-3-(biphenyl-4-ylmethylamino)benzamide, and the mixture was stirred at room temperature for 100 hours and then at 50° C. for 30 hours. The reaction solution was extracted with chloroform and with water. The organic layer was washed six times with water, and was concentrated. The residue was purified through silica-gel column chromatography (eluent: a mixture of ethyl acetate and methanol at a ratio of 9:1) to give 0.135 g of 2-amino-6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)benzimidazole (231).

Properties of Compound (231):

^{1}H-NMR(DMSO-d6, δ): 5.32(2H, s), 6.77(2H, s), 7.05 (1H, d, J=8.8 Hz), 7.21(2H, d, J=8.3 Hz), 7.31–7.38(4H, m), 7.43(2H, t, J=7.5 Hz), 7.58–7.65(6H, m), 7.79–7.82(2H, m).

IR(KBr): 1684 cm^{-1}.

Mass(FAB): m/e 483(M+1).

mp: 352.5–355.0° C.

EXAMPLE 170

Synthesis of 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-n-propylbenzimidazole potassium salt (232)

Triethylamine (0.060 g) and 0.084 g of butyryl chloride were added to a solution of 0.300 g of N-benzenesulfonyl-4-amino-3-(biphenyl-4-ylmethylamino)benzamide in 2 ml of N,N-dimethylformamide, and the mixture was stirred at room temperature for 1.5 hours. The reaction solution was directly purified through silica-gel column chromatography to obtain 0.250 g of N-benzenesulfonyl-3-(biphenyl-4-ylmethylamino)-4-butyrylaminobenzamide. To this compound were added 5 ml of methanol and 0.50 g of 35% hydrochloric acid, and the mixture was stirred at 60° C. for 3 hours. Then, 20% potassium hydrogencarbonate was added thereto to stop the reaction, and the reaction solution was extracted with ethyl acetate and with water. The organic layer was concentrated, and the product was dissolved in a small amount of chloroform. Ether was added thereto for crystallization. The crystals precipitated were separated through filtration, and were dried to give 0.157 g of 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-n-propylbenzimidazole potassium salt (232).

Properties of Compound (232):

^{1}H-NMR(DMSO-d6, δ): 0.95(3H, t, J=7.4 Hz), 1.77(2H, q, J=7.5 Hz), 2.82(2H, t, J=7.5 Hz), 5.55(2H, s), 7.11(2H, d, J=8.2 Hz), 7.32–7.38(4H, m), 7.43(2H, t, J=7.5 Hz), 7.47 (1H, d, J=8.4 Hz), 7.58–7.64(4H, m), 7.79–7.83(3H, m), 7.96(1H, s).

IR(Nujol): 1592 cm^{-1}.

Mass(FAB): m/e 548(M+1).

mp: 279.0–282.0° C.

EXAMPLE 171

Synthesis of 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-n-heptylbenzimidazole (233)

In the same manner as in Example 170, 0.232 g of 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-n-heptylbenzimidazole (233) were formed from 0.400 g of N-benzenesulfonyl-4-amino-3-(biphenyl-4-ylmethylamino) benzamide, 0.080 g of triethylamine and 0.170 g of octanoyl chloride.

Properties of Compound (233):

^{1}H-NMR(DMSO-d6, δ): 0.79(3H, t, J=7.3 Hz), 1.12–1.24 (6H, m), 1.24–1.31(2H, m), 1.66–1.73(2H, m), 2.84(2H, t, J=7.6 Hz), 5.58(2H, s), 7.14(2H, d, J=8.1 Hz), 7.34(2H, t, J=7.6 Hz), 7.43(2H, t, J=7.4 Hz), 7.52–7.66(7H, m), 7.75 (1H, d, J=8.8 Hz), 7.95(2H, d, J=7.6 Hz), 8.15(1H, s), 12.45(1H, s). IR(KBr): 1688 cm^{-1}.

mp: 112.0–117.5° C.

EXAMPLE 172

Synthesis of 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-chloromethylbenzimidazole (234)

In the same manner as in Example 170, 0.913 g of 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-chloromethylbenzimidazole (234) were formed from 0.300 g of N-benzenesulfonyl-4-amino-3-(biphenyl-4-ylmethylamino)benzamide, 0.060 g of triethylamine and 0.102 of chloroacetyl chloride.

Properties of Compound (234):

^{1}H-NMR(DMSO-d6, δ): 5.10(2H, s), 5.71(2H, s), 7.23 (2H, d, J=8.3 Hz), 7.35(1H, t, J=7.3 Hz), 7.44(2H, t, J=7.5 Hz), 7.60–7.66(6H, m), 7.69(1H, t, J=7.5 Hz), 7.75–7.81 (2H, m), 7.98–8.01(2H, m), 8.16(1H, s), 12.52(1H, s).

IR(KBr): 1700 cm^{-1}.

mp: 220.5–223.5° C.

EXAMPLE 173

Synthesis of 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-methoxymethylbenzimidazole (235)

In the same manner as in Example 170, 0.183 g of 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-methoxymethylbenzimidazole (235) were formed from 0.400 g of N-benzenesulfonyl-4-amino-3-(biphenyl-4-ylmethylamino)benzamide, 0.115 g of triethylamine and 0.131 g of methoxyacetyl chloride.

Properties of Compound (235):

^{1}H-NMR(DMSO-d6, δ): 3.31(3H, s), 4.72(2H, s), 5.63 (2H, s), 7.23(2H, d, J=8.3 Hz), 7.35(1H, t, J=7.4 Hz), 7.44(2H, t, J=7.5 Hz), 7.60–7.65(6H, m), 7.70(1H, t, J=7.5 Hz), 7.72–7.79(2H, m), 7.98– 8.01(2H, m), 8.18(1H, s), 12.50(1H, s).

IR(KBr): 1690 cm^{-1}.

mp: 195.0–198.0° C.

EXAMPLE 174

Synthesis of 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-i-propylbenzimidazole potassium salt (236)

In the same manner as in Example 170, 0.400 g of N-benzenesulfonyl-4-amino-3-(biphenyl-4-ylmethylamino) benzamide, 0.080 g of triethylamine and 0.112 g of isobutyryl chloride were reacted as starting materials. The crude product was dissolved in a mixed solvent of methanol and a 20% potassium hydrogencarbonate aqueous solution, and the pH was adjusted to 7 with 10% hydrochloric acid. The crystals precipitated were crystals of 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-i-propylbenzimidazole potassium salt [(236), 0.167 g].

Properties of Compound (236):

^{1}H-NMR(DMSO-d6, δ): 1.26(6H, d, J=6.8 Hz), 3.25–3.40(1H, m), 5.58(2H, s), 7.09(2H, d, J=8.3 Hz), 7.32–7.37(4H, m), 7.43(2H, t, J=7.5 Hz), 7.48(1H, d, J=8.4 Hz), 7.58–7.64(4H, m), 7.79–7.83(3H, m), 7.95(1H, s).

IR(Nujol): 1592 cm^{-1}.

Mass(FAB): m/e 548(M+1).

mp: 310.1–312.7° C.

EXAMPLE 175

Synthesis of 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl-2-methylthiobenzimidazole (237)

A 20% potassium hydroxide aqueous solution (0.323 g), 2 ml of water and 0.123 g of methyl iodide were added to a solution of 0.310 g of 6-benzenesulfonylcarbamoyl-1-

(biphenyl-4-ylmethyl)-2-mercaptobenzimidazole in 5 ml of methanol in this order, and the mixture was stirred at room temperature for 2 hours. The reaction solution was adjusted to a pH of from 5 to 6 with 10% hydrochloric acid. The crystals precipitated were separated through filtration, and were dried to give 0.281 g of 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-methylthiobenzimidazole (237).

Properties of Compound (237):

^{1}H-NMR(DMSO-d6, δ): 2.75(3H, s), 5.48(2H, s), 7.25 (2H, d, J=8.3 Hz), 7.35(1H, t, J=7.4 Hz), 7.44(2H, t, J=7.5 Hz), 7.60–7.66(7H, m), 7.68–7.75(2H, m), 7.82–7.99(2H, m), 8.19(1H, d, J=1.6 Hz), 12.43(1H, s).

IR(KBr): 1685 cm^{-1}.

mp: 218.8–220.4° C.

EXAMPLE 176

Synthesis of 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-ethylthiobenzimidazole (238)

In the same manner as in Example 175, 0.225 g of 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-ethylthiobenzimidazole (238) were formed from 0.240 g of 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-mercaptobenzimidazole and 0.117 g of ethyl iodide.

Properties of Compound (238):

^{1}H-NMR(DMSO-d6, δ): 1.39(3H, t, J=7.3 Hz), 3.37(2H, q, J=7.3 Hz), 5.47(2H, s), 7.24(2H, d, J=8.1 Hz), 7.35(1H, t, J=7.1 Hz), 7.44(2H, t, J=7.6 Hz), 7.57–7.68(8H, m), 7.75(1H, d, J=8.4 Hz), 7.98(2H, d, J=7.5 Hz), 8.15(1H, s), 12.43(1H, s).

IR(KBr): 1686 cm^{-1}.

mp: 125.5–129.5° C.

EXAMPLE 177

Synthesis of 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-n-propylthiobenzimidazole (239)

In the same manner as in Example 175, 0.156 g of 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-n-propylthiobenzimidazole (239) were formed from 0.220 g of 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-mercaptobenzimidazole and 0.117 g of n-propyl iodide.

Properties of Compound (239):

^{1}H-NMR(DMSO-d6, δ): 0.97(3H, t, J=7.4 Hz), 1.76(2H, q, J=7.2 Hz), 3.29–3.36(2H, m), 5.48(2H, s), 7.24(2H, d, J=8.3 Hz), 7.35(1H, t, J=7.3 Hz), 7.44(2H, t, J=7.4 Hz), 7.58–7.71(8H, m), 7.74(1H, dd, J=8.5 and 1.7 Hz), 7.99(2H, d, J=7.7 Hz), 8.17(1H, s), 12.43(1H, s).

IR(KBr): 1690 cm^{-1}.

mp: 106.0–111.5° C.

EXAMPLE 178

Synthesis of 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-n-hexylthiobenzimidazole (240)

In the same manner as in Example 175, 0.212 g of 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-n-hexylthiobenzimidazole (240) were formed from 0.250 g of 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-mercaptobenzimidazole and 0.166 g of n-hexyl iodide.

Properties of Compound (240):

^{1}H-NMR(DMSO-d6, δ): 0.82(3H, t, J=7.9 Hz), 1.19–1.33 (4H, m), 1.33–1.44(2H, m), 1.68–1.75(2H, m), 3.30–3.43 (2H, m), 5.48(2H, s), 7.23(2H, d, J=8.2 Hz), 7.35(1H, t, J=7.1 Hz), 7.44(2H, t, J=7.6 Hz), 7.60–7.75(9H, m), 8.00 (2H, d, J=7.7 Hz), 8.19(1H, s), 12.44(1H, s).

IR(KBr): 1688 cm^{-1}.

mp: 139.5–141.0° C.(decomp.).

EXAMPLE 179

Synthesis of 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)benzimidazole (241)

A mixture of 0.400 g of N-benzenesulfonyl-4-amino-3-(biphenyl-4-ylmethylamino)benzamide and 2 ml of formic acid was stirred at 90° C. for 3 hours. The reaction solution was concentrated, and was precipitated with methanol. The crystals precipitated were separated through filtration, and were dried to give 0.243 g of 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)benzimidazole (241).

Properties of Compound (241):

^{1}H-NMR(DMSO-d6, δ): 5.60(2H, s), 7.35(1H, t, J=7.2 Hz), 7.39(2H, d, J=8.2 Hz), 7.44(2H, t, J=7.6 Hz), 7.61–7.77 (9H, m), 8.00(2H, d, J=7.7 Hz), 8.26(1H, s), 8.66(1H, s), 12.5(1H, s).

IR(KBr): 1683 cm^{-1}.

mp: 141.5–143.6° C.

EXAMPLE 180

Synthesis of 1-(4-benzyloxybenzyl)-2-methyl-6-[(2-pyridylmethyl)carbamoyl]benzimidazole (242)

Four milliliters of acetic acid and 8 ml of ethanol were added to 0.434 g of N-(2-pyridylmethyl)-4-acetylamino-3-(4-benzyloxybenzylamino)benzamide, and the mixture was stirred at 90° C. for 7 hours. The reaction solution was concentrated under reduced pressure. Ethyl acetate and ether were added to the residue for crystallization. The crystals were separated through filtration, and were dried to give 0.375 g of 1-(4-benzyloxybenzyl)-2-methyl-6-[(2-pyridylmethyl)carbamoyl]benzimidazole (242).

Properties of Compound (242):

^{1}H-NMR($CDCl_3$, δ): 2.59(3H, s), 4.78(2H, d, J=4.8 Hz), 5.01(2H, s), 5.31(2H, s), 6.89(2H, d, J=8.7 Hz), 6.99(2H, d, J=8.6 Hz), 7.21(1H, dd, J=5.1 and 7.4 Hz), 7.29–7.42(6H, m), 7.62(1H, br t), 7.65–7.75(3H, m), 7.98(1H, s), 8.57(1H, d, J=4.1 Hz).

IR(KBr): 1640 cm^{-1}.

mp: 169.0–170.0° C.

EXAMPLE 181

Synthesis of 2-methyl-1-(3,4-methylenedioxybenzyl)-6-[(2-pyridylmethyl) carbamoyl]benzimidazole (243)

Two milliliters of acetic acid and 5 ml of methanol were added to 0.490 g of N-(2-pyridylmethyl)-4-acetylamino-3-(3,4-methylenedioxybenzylamino)benzamide, and the mixture was stirred at 70° C. for 8 hours. The reaction solution was concentrated under reduced pressure. The residue was purified through silica-gel column chromatography (eluent: a mixture of ethyl acetate and methanol at a ratio of 9:1), and was then crystallized from ethyl acetate. The crystals were separated through filtration, and were dried to give 0.270 g of 2-methyl-1-(3,4-methylenedioxybenzyl)-6-[(2-pyridylmethyl)carbamoyl]benzimidazole (243).

Properties of Compound (243):

^{1}H-NMR($CDCl_3$, δ): 2.59(3H, s), 4.78(2H, d, J=4.8 Hz), 5.28(2H, s), 5.93(2H, s), 6.51(1H, d, J=1.6 Hz), 6.55(1H, dd, J=1.4 and 7.9 Hz), 6.72(2H, d, J=8.0 Hz), 7.22(1H, dd, J=6.7 and 5.0 Hz), 7.34(1H, d, J=7.7 Hz), 7.62(1H, br t), 7.67–7.75 (3H, m), 7.96(1H, d, J=1.1 Hz), 8.58(1H, d, J=4.9 Hz).

IR(KBr): 1637 cm^{-1}.

mp: 190.5–192.0° C.

EXAMPLE 182

Synthesis of 2-methyl-6-[(2-pyridylmethyl) carbamoyl]-1-[4-(1,2,3-thiadiazol-4-yl)benzyl] benzimidazole (244)

In the same manner as in Example 180, 0.33 g of 2-methyl-6-[(2-pyridylmethyl)carbamoyl]-1-[4-(1,2,3-thiadiazol-4-yl)benzyl]benzimidazole (244) were formed from 0.50 g of N-(2-pyridylmethyl)-4-acetylamino-3-[4-(1,2,3-thiadiazol-4-yl)benzylamino]benzamide.

Properties of Compound (244):

^{1}H-NMR($CDCl_3$, δ): 2.58(3H, s), 4.58(2H, d, J=5.9 Hz), 5.62(2H, s), 7.24(1H, dd, J=7.3 and 5.0 Hz), 7.28–7.33(3H, m), 7.64(1H, d, J=8.4 Hz), 7.73(1H, dt, J=7.7 and 1.6 Hz), 7.81(1H, dd, J=8.4 and 1.3 Hz), 8.10(1H, d, J=8.2 Hz), 8.13(1H, s), 8.49(1H, d, J=4.2 Hz), 9.04(1H, t, J=5.9 Hz), 9.58(1H, s).

IR(KBr): 1642 cm^{-1}.

mp: 216.0–217.0° C.

EXAMPLE 183

Synthesis of 6-benzenesulfonylcarbamoyl-1-(2,4-difluorobenzyl-2-methylbenzimidazole (245)

N-benzenesulfonyl-4-acetylamino-3-(2,4-difluorobenzylamino)benzamide (0.370 g) was dissolved in a mixed solvent of 3.3 g of 10% hydrochloric acid, 6 ml of methanol and 4 ml of water, and 0.5 g of 35% hydrochloric acid were further added thereto. The mixture was stirred at 60° C. for 3 hours. A 20% potassium hydrogencarbonate aqueous solution was added to the reaction solution to render it basic. Then, this solution was adjusted to a pH of from 5 to 6 with 10% hydrochloric acid. The crystals precipitated were separated through filtration, and were dried to give 0.182 g of 6-benzenesulfonylcarbamoyl-1-(2,4-difluorobenzyl-2-methylbenzimidazole

Properties of Compound (245):

^{1}H-NMR(DMSO-d6, δ): 2.53(3H, s), 5.56(2H, s), 6.95–7.01(1H, m), 7.04(1H, dt, J=8.7 and 1.4 Hz), 7.32(1H, dt, J=10.7 and 2.1 Hz), 7.59–7.66(3H, m), 7.68–7.74(2H, m), 8.00(2H, d, J=8.1 Hz), 8.13(1H, s), 12.43(1H, s). IR(KBr): 1686 cm^{-1}.

mp: 234.5–235.5° C.(decomp.).

EXAMPLE 184

Synthesis of 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-phenylbenzimidazole (246)

Triethylamine (0.115 g) and 0.200 g of benzoyl chloride were added to a solution of 0.500 g of N-benzenesulfonyl-4-amino-3-(biphenyl-4-ylmethylamino)benzamide in 5 ml of N,N-dimethylformamide. The mixture was stirred at room temperature for 15 hours. A potassium hydrogencarbonate aqueous solution was added thereto to stop the reaction. The solvent was distilled off under reduced pressure. The residue was dissolved in a mixture of water and methanol, and the solution was adjusted to a pH of from 5 to 6 with 10% hydrochloric acid. The crystals precipitated were collected, and were dried to obtain 0.393 g of crude N-benzenesulfonyl-4-benzoylamino-3-(biphenyl-4-ylmethylamino)benzamide. This crude product was converted to 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-phenylbenzimidazole [(246), 0.270 g] in the same manner as in Example 183.

Properties of Compound (246):

^{1}H-NMR(DMSO-d6, δ): 5.70(2H, s), 7.07(2H, d, J=8.2 Hz), 7.32–7.37(1H, m), 7.43(2H, t, J=5.7 Hz), 7.53–7.58 (2H, m), 7.58–7.65(7H, m), 7.68–7.72(1H, m), 7.77(2H, dd, J=7.5 and 1.5 Hz), 7.81–7.83(2H, m), 7.98–8.02(2H, m), 8.22(1H, s), 12.47(1H, s).

IR(KBr): 1690 cm^{-1}.

mp: 138.5–139.5° C.

EXAMPLE 185

Synthesis of 6-benzenesulfonylcarbamoyl-2-methyl-1-(2-nitrobenzyl)benzimidazole (247)

In the same manner as in Example 183, 0.237 g of 6-benzenesulfonylcarbamoyl-2-methyl-1-(2-nitrobenzyl) benzimidazole (247) were formed from 0.79 g of N-benzenesulfonyl-4-acetylamino-3-(2-nitrobenzylamino) benzamide.

Properties of Compound (247):

^{1}H-NMR(DMSO-d6, δ): 2.48(3H, s), 5.01(2H, s), 5.93 (2H, s), 6.28–6.30(1H, m), 7.55–7.62(4H, m), 7.64–7.74 (3H, m), 7.97(2H, d, J=8.0 Hz), 8.10(1H, s), 8.22–8.28(1H, m), 12.39(1H, s).

IR(KBr): 1686 cm^{-1}.

mp: 269.5–272.5(decomp.).

EXAMPLE 186

Synthesis of 6-benzenesulfonylcarbamoyl-2-methyl-1-benzylbenzimidazole (248)

In the same manner as in Example 183, 0.222 g of 6-benzenesulfonylcarbamoyl-2-methyl-1-benzylbenzimidazole (248) were formed from 0.38 g of N-benzenesulfonyl-4-acetylamino-3-benzylaminobenzamide.

Properties of Compound (248):

^{1}H-NMR(DMSO-d6, δ): 2.54(3H, s), 5.55(2H, s), 7.12 (2H, d, J=7.9 Hz), 7.28(1H, t, J=7.3 Hz), 7.34(2H, t, J=7.0 Hz), 7.61–7.66(3H, m), 7.69–7.76(2H, m), 8.00(2H, d, J=7.9 Hz), 8.18(1H, s), 12.43(1H, s).

IR(KBr): 1695 cm^{-1}.

mp: 260.0–262.0° C.(decomp.).

EXAMPLES 187 AND 188

Synthesis of 6-benzenesulfonylcarbamoyl-2-methyl-1-(4-nitrobenzyl)benzimidazole (249) and 6-benzenesulfonylcarbamoyl-2-methyl-1-(4-nitrobenzyl)benzimidazole potassium salt (250)

In the same manner as in Example 183, 0.255 g of 6-benzenesulfonylcarbamoyl-2-methyl-1-(4-nitrobenzyl) benzimidazole (249) were formed as a crystal from 0.505 g of N-benzenesulfonyl-4-acetylamino-3-(4-nitrobenzylamino)benzamide. Further, the filtrate was concentrated to form 0.136 g of 6-benzenesulfonylcarbamoyl-

2-methyl-1-(4-nitrobenzyl)benzimidazole potassium salt (250) as a crystal.

Properties of Compound (249):

^{1}H-NMR(DMSO-d6, δ): 2.50(3H, s), 5.70(2H, s), 7.30 (2H, d, J=8.7 Hz), 7.52(2H, t, J=7.6 Hz), 7.57(2H, d, J=8.3 Hz), 7.76(1H, dd, J=8.4 and 1.4 Hz), 7.92(2H, d, J=7.3 Hz), 8.05(1H, s), 8.20(2H, d, J=8.7 Hz), 12.43(1H, s).

IR(KBr): 1686 cm.

mp: 164.5–167.0° C.

Properties of Compound (250):

^{1}H-NMR(DMSO-d6, δ): 2.51(3H, s), 5.68(2H, s), 7.28 (2H, d, J=8.5 Hz), 7.32–7.41(3H, m), 7.46(1H, d, J=8.4 Hz), 7.78–7.86(3H, m), 7.91(1H, s), 8.20(2H, d, J=8.5 Hz).

IR(KBr): 1594 cm^{-1}.

mp: 326.0–328.0° C.(decomp.).

EXAMPLE 189

Synthesis of 6-benzenesulfonylcarbamoyl-1-(4-benzyloxybenzyl)-2-methylbenzimidazole (251)

A mixture containing 0.500 g of N-benzenesulfonyl-3-amino-4-acetylaminobenzamide potassium salt, 0.470 g of 4-benzyloxybenzyl bromide, 0.925 g of a 20% potassium hydrogencarbonate aqueous solution and 3 ml of N,N-dimethylformamide was stirred at 90° C. for 1 hour. The reaction solution was concentrated, and was purified through silica-gel column chromatography (eluent: a mixture of ethyl acetate and methanol at a ratio of 9:1) to obtain crude N-benzenesulfonyl-4-acetylamino-3-(4-benzyloxybenzylamino)benzamide. This crude product was cyclized in the same manner as in Example 183 to give 0.160 g of 6-benzenesulfonylcarbamoyl-1-(4-benzyloxybenzyl)-2-methylbenzimidazole (251).

Properties of Compound (251):

^{1}H-NMR(DMSO-d6, δ): 2.54(3H, s), 5.05(2H, s), 5.44 (2H, s), 7.09(2H, d, J=8.7 Hz), 7.32(2H, d, J=7.0 Hz), 7.29–7.44(5H, m), 7.58–7.67(3H, m), 7.68–7.75(2H, m), 7.79–8.02(2H, m), 8.18(1H, s), 12.46(1H, s).

IR(KBr): 1685 cm^{-1}.

mp: 111.0–114.0° C.

EXAMPLE 190

Synthesis of 2-methyl-5-[(2-pyridylmethyl) carbamoyl]benzimidazole (252)

Five-percent palladium on carbon (0.10 g) was added to a mixture of 1.00 g of crude N-(2-pyridylmethyl)-4-acetylamino-3-nitrobenzamide, 8 ml of acetic acid and 12 ml of ethanol, and the solution was stirred in a hydrogen atmosphere at 80° C. for 7 hours. The solid material was separated through filtration, and the filtrate was concentrated. Ethyl acetate was added to the residue for crystallization. The crystals were separated through filtration, and were dried to give 0.57 g of 2-methyl-5-[(2-pyridylmethyl) carbamoyl]benzimidazole (252).

Properties of Compound (252):

^{1}H-NMR($CDCl_3$, δ): 2.52(3H, s), 4.59(2H, d, J=5.9 Hz), 7.26(1H, dd, J=7.1 and 5.1 Hz), 7.33(1H, d, J=7.8 Hz), 7.50(1H, d, J=8.4 Hz), 7.72–7.78(2H, m), 8.08(1H, s), 8.51(1H, d, J=4.8 Hz), 9.04(1H, t, J=5.8 Hz), 12.44(1H, s).

IR(KBr): 1641 cm^{-1}.

mp: 212.0–215.0° C.

EXAMPLES 191 AND 192

Synthesis of 1-benzenesulfonyl-2-methyl-6-[(2-pyridylmethyl)carbamoyl]benzimidazole (253) and 1-benzenesulfonyl-2-methyl-5-[2-pyridylmethyl) carbamoyl]benzimidazole (254)

Ten milliliters of dichloromethane and 0.760 g of triethylamine were added to 1.00 g of 1-methyl-5-[(2-pyridylmethyl)carbamoyl]benzimidazole, and 0.994 g of benzenesulfonyl chloride were added dropwise thereto. The mixture was stirred for 3 hours, and the reaction solution was washed three times with water and then with a sodium hydrogencarbonate aqueous solution. The organic layer was concentrated under reduced pressure, and was purified through silica-gel column chromatography (eluent: a mixture of ethyl acetate and methanol at a ratio of 9:1) to obtain 1.380 g of a mixture of 1-benzenesulfonyl-2-methyl-6-[(2-pyridylmethyl)carbamoyl]benzimidazole and 1-benzenesulfonyl-2-methyl-5-(2-pyridylmethyl) carbamoyl]benzimidazole. This mixture was further purified through medium-pressure silica-gel column chromatography (eluent: a mixture of ethyl acetate and methanol at a ratio of 100:3) to give 0.550 g of oily 1-benzenesulfonyl-2-methyl-6-[(2-pyridylmethyl)carbamoyl]benzimidazole (253) and 0.540 g of oily 1-benzenesulfonyl-2-methyl-5-[2-pyridylmethyl)carbamoyl]benzimidazole (254). These oily products were dissolved in 1.5 ml of methylene chloride, and were crystallized from diethyl ether.

Properties of Compound (253):

^{1}H-NMR($CDCl_3$, δ): 2.84(3H, s), 4.81(2H, d, J=4.8 Hz), 7.24(1H, dd, J=5.1 and 7.3 Hz), 7.37(1H, d, J=7.7 Hz), 7.53(2H, dd, J=7.9 and 7.5 Hz), 7.63–7.74(2H, m), 7.85(1H, dd, J=8.4 and 1.2 Hz), 7.97(2H, dd, J=9.6 and 1.1 Hz), 8.58–8.61(2H, m).

IR(KBr): 1636 cm^{-1}.

mp: 163.4–164.3° C.

Properties of Compound (254):

^{1}H-NMR($CDCl_3$, δ):2.83(3H, s), 4.78(2H, d, J=4.7 Hz), 7.23(1H, dd, J=4.9 and 8.6 Hz), 7.34(1H, d, J=7.9 Hz), 7.53(2H, dd, J=7.5 and 8.4 Hz), 7.64–7.75(3H, m), 7.91–7.96(3H, m),8.10(1H, d, J=9.1 Hz), 8.14(1H, d, J=1.3 Hz), 8.56(1H, dd, J=4.9 and 1.0 Hz).

IR(KBr): 1657 cm^{-1}.

mp: 88.3–91.3° C.

EXAMPLES 193 AND 194

Synthesis of 2-methyl-1-(4-nitrobenzyl)-6-[(2-pyridylmethyl)carbamoyl]benzimidazole (255) and 2-methyl-1-(4-nitrobenzyl)-5-[(2-pyridylmethyl) carbamoyl]benzimidazole (256)

Ten milliliters of N,N-dimethylformamide, 3.24 g of 4-nitrobenzyl bromide and 2.52 g of sodium hydrogencarbonate were added to 3.56 g of 2-methyl-5-[2-pyridylmethyl)carbamoyl]benzimidazole, and the mixture was heated at 80° C. for 2 hours. The reaction solution was separated with the addition of chloroform and water. The organic layer was concentrated under reduced pressure, and was purified through silica-gel column chromatography (eluent: a mixture of ethyl acetate and methanol at a ratio of 4:1) to obtain a mixture of 2-methyl-1-(4-nitrobenzyl)-6-[(2-pyridylmethyl)carbamoyl]benzimidazole and 2-methyl-1-(4-nitrobenzyl)-5-[(2-pyridylmethyl)carbamoyl] benzimidazole. This mixture was further separated into position isomers through medium-pressure silica-gel column chromatography (eluent: a mixture of ethyl acetate and methanol at a ratio of 85:15). Each of the position isomers was recrystallized from a mixed solvent of chloroform and diethyl ether to give 1.37 g of 2-methyl-1-(4-nitrobenzyl)-6-[(2-pyridylmethyl)carbamoyl]benzimidazole (255) and 1.19 g of 2-methyl-1-(4-nitrobenzyl)-5-[(2-pyridylmethyl) carbamoyl]benzimidazole (256).

Properties of Compound (255):

^{1}H-NMR($CDCl_3$, δ): 2.59(3H, s), 4.77(2H, d, J=4.8 Hz), 5.48(2H, s), 7.09(2H, d, J=8.7 Hz), 7.22(1H, dd, J=7.2 and 4.9 Hz), 7.33(1H, d, J=7.8 Hz), 7.66–7.70(2H, m), 7.73(1H, dd, J=8.4 and 1.5 Hz), 7.78(1H, d, J=8.4 Hz), 7.91(1H, d, J=1.2 Hz), 8.15–8.19(2H, m), 8.56(1H, d, J=4.6 Hz).

IR(KBr): 1652 cm^{-1}.

mp: 116.1–119.1° C.

Properties of Compound (256):

^{1}H-NMR($CDCl_3$, δ): 2.59(3H, s), 4.79(2H, d, J=4.8 Hz), 5.46(2H, s), 7.17–7.24(4H, m), 7.35(1H, d, J=7.8 Hz), 7.69(2H, dt, J=7.6 and 1.7 Hz), 7.83(1H, d, J=8.4 Hz), 8.19(2H, d, J=8.6 Hz), 8.26(1H, d, J=1.3 Hz), 8.57(1H, d, J=4.8 Hz)

IR(KBr): 1634 cm^{-1}.

mp: 203.7–206.3° C.

EXAMPLES 195 AND 196

Synthesis of 2-methyl-1-(2-phenylethyl)-6-[(2-pyridylmethyl)carbamoyl]benzimidazole (257) and 2-methyl-1-(2-phenylethyl)-5-(2-pyridylmethyl) carbamoyl]benzimidazole (258)

In the same manner as in Examples 193 and 194, 0.30 g of 2-Methyl-1-(2-phenylethyl)-6-[(2-pyridylmethyl) carbamoyl]benzimidazole (257) and 0.23 g of 2-methyl-1-(2-phenylethyl)-5-[(2-pyridylmethyl)carbamoyl] benzimidazole (258) were formed from 2.00 g of 2-methyl-5-[(2-pyridylmethyl)carbamoyl]benzimidazole and 15.0 g of phenetyl iodide.

Properties of Compound (257):

^{1}H-NMR($CDCl_3$, δ): 2.17(3H, s), 3.10(2H, t, J=6.8 Hz), 4.35(2H, t, J=6.8 Hz), 4.82(2H, d, J=4.8 Hz), 6.92–6.97(2H, m), 7.21–7.28(4H, m), 7.38(1H, d, J=7.8 Hz), 7.78(1H, br t), 7.68–7.73(3H, m), 7.98(1H, d, J=0.9 Hz), 8.60(1H, dd, J=1.0 and 4.9 Hz).

IR(neat): 1633 cm^{-1}.

liquid.

Properties of Compound (258):

^{1}H-NMR($CDCl_3$, δ): 2.19(3H, s), 3.08(2H, t, J=6.8 Hz), 4.35(2H, t, J=6.8 Hz), 4.81(2H, d, J=4.8 Hz), 6.91–6.96(2H, m), 7.19–7.26(4H, m), 7.31(1H, d, J=8.4 Hz), 7.36(1H, d, J=7.8 Hz), 7.64–7.73(2H, m), 7.85(1H, dd, J=1.7 and 8.4 Hz), 8.19(1H, d, J=1.3 Hz), 8.58(1H, d, J=4.0 Hz).

IR(neat): 1643 cm^{-1}.

liquid.

EXAMPLES 197 AND 198

Synthesis of 1-(2,4-difluorobenzyl)-2-methyl-6-[(2-pyridylmethyl)carbamoyl]benzimidazole (259) and 1-(2,4-difluorobenzyl)-2-methyl-5-[(2-pyridylmethyl)carbamoyl]benzimidazole (260)

In the same manner as in Examples 193 and 194, 0.25 g of 1-(2,4-difluorobenzyl)-2-methyl-6-[(2-pyridylmethyl) carbamoyl]benzimidazole (259) and 0.25 g of 1-(2,4-difluorobenzyl)-2-methyl-5-[(2-pyridylmethyl)carbamoyl] benzimidazole (260) were formed from 1.00 g of 2-methyl-5-[(2-pyridylmethyl)carbamoyl]benzimidazole and 1.00 g of 2,4-difluorobenzyl bromide.

Properties of Compound (259):

^{1}H-NMR($CDCl_3$, δ): 2.62(3H, s), 4.78(2H, d, J=4.7 Hz), 5.38(2H, s), 6.73–6.79(2H, m), 6.88(1H, t, J=10.0 Hz), 7.24(1H, dd, J=7.3 and 5.1 Hz), 7.35(1H, d, J=7.8 Hz), 7.67–7.76(4H, m), 7.97(1H, s), 8.58(1H, d, J=4.4 Hz). IR(KBr): 1642 cm^{-1}.

mp: 98.0–104.0° C.

Properties of Compound (260):

^{1}H-NMR($CDCl_3$, δ): 2.62(3H, s), 4.79(2H, d, J=4.7 Hz), 5.35(2H, s), 6.72–6.81(2H, m), 6.89(1H, t, J=9.8 Hz), 7.22 (1H, t, J=6.2 Hz), 7.28(1H, d, J=8.4 Hz), 7.34(1H, d, J=7.8 Hz), 7.63–7.71(2H, m), 7.83(1H, d, J=8.4 Hz), 7.97(1H, s), 8.57(1H, d, J=4.7 Hz).

IR(KBr): 1647 cm^{-1}.

mp: 143.5–144.0° C.

EXAMPLES 199 AND 200

Synthesis of 1-(4-aminobenzyl)-2-methyl-6-[(2-pyridylmethyl)carbamoyl]benzimidazole (261) and 1-(4-aminobenzyl)-2-methyl-5-[(2-pyridylmethyl) carbamoyl]benzimidazole (262)

Thirty milliliters of methanol and 0.20 g of 5% palladium on carbon were added to 2.32 g of a mixture of 2-methyl-1-(4-nitrobenzyl)-6-[(2-pyridylmethyl)carbamoyl] benzimidazole and 2-methyl-1-(4-nitrobenzyl)-5-[(2-pyridylmethyl)carbamoyl]benzimidazole, and the mixture was stirred in a hydrogen atmosphere at room temperature until the starting material disappeared. The solid material was separated through filtration, and the filtrate was concentrated. The resulting residue was purified through medium-pressure silica-gel column chromatography (eluent: a mixture of ethyl acetate and methanol at a ratio of 85:15) to separate 1-(4-aminobenzyl)-2-methyl-6-[(2-pyridylmethyl)carbamoyl]benzimidazole and 1-(4-aminobenzyl)-2-methyl-5-[(2-pyridylmethyl)carbamoyl] benzimidazole. Each of these compounds was crystallized from a mixed solvent of chloroform and diethyl ether. The crystals were separated through filtration, and were dried to give 0.354 g of 1-(4-aminobenzyl)-2-methyl-6-[(2-pyridylmethyl)carbamoyl]benzimidazole (261) and 0.330 g of 1-(4-aminobenzyl)-2-methyl-5-[(2-pyridylmethyl) carbamoyl]benzimidazole (262).

Properties of Compound (261):

^{1}H-NMR($CDCl_3$, δ): 3.00(3H, s), 4.98(2H, s), 5.88(2H, s), 7.55(2H, d, J=8.6 Hz), 7.69(2H, d, J=8.6 Hz), 7.90(1H, d, J=8.6 Hz), 7.96(1H, dt, J=7.1 and 0.6 Hz), 8.12(1H, J=8.0 Hz), 8.18(1H, dd, J=8.5 and 1.4 Hz), 8.55(1H, dt, J=8.0 and 1.7 Hz), 8.62(1H, d, J=1.1 Hz), 8.77(1H, dd, J=5.9 and 1.1 Hz).

IR(KBr): 1643 cm^{-1}.

mp: 180.0–181.0° C.

Properties of Compound (262):

^{1}H-NMR($CDCl_3$, δ): 3.00(3H, s), 5.01(2H, s), 5.83(2H, s), 7.47(2H, d, J=8.5 Hz), 7.78(2H, d, J=8.5 Hz), 7.78(1H, d, J=8.9 Hz), 7.97(1H, dt, J=7.2 and 0.7 Hz), 8.13(1H, J=8.1 Hz), 8.15(1H, d, J=8.9 Hz), 8.51(1H, s), 8.55(1H, dt, J=7.9 and 1.6 Hz), 8.77(1H, d, J=5.8 Hz).

IR(KBr): 1639, 1612 cm^{-1}.

mp: 168.0–171.0° C.

EXAMPLE 201

Synthesis of 1-[4-(benzenesulfonylamino)benzyl]-2-methyl-6-[(2-pyridylmethyl)carbamoyl] benzimidazole (263)

Triethylamine (0.185 g) and benzenesulfonyl chloride (0.210 g) were added to a solution of 0.340 g of 1-(4-

aminobenzyl)-2-methyl-6-[(2-pyridylmethyl)carbamoyl] benzimidazole in 10 ml of chloroform, and the mixture was stirred at room temperature for 8 hours. Water was added thereto to stop the reaction, and the reaction mixture was extracted with chloroform. The organic layer was washed three times with water, dried, and concentrated. The residue was then purified through silica-gel column chromatography (eluent: a mixture of ethyl acetate and methanol at a ratio of 100:1 to 4:1) to give 0.300 g of 1-[4-(benzenesulfonylamino)benzyl]-2-methyl-6-[(2-pyridylmethyl)carbamoyl]benzimidazole (263).

Properties of Compound (263):

^{1}H-NMR($CDCl_3$, δ): 2.53(3H, s), 4.78(2H, d, J=4.8 Hz), 5.28(2H, s), 6.90(2H, t, J=8.6 Hz), 6.99(2H, d, J=8.5 Hz), 7.11(1H, s), 7.23(1H, dd, J=5.5 and 7.2 Hz), 7.34(1H, d, J=7.7 Hz), 7.40(2H, t, J=8.1 Hz), 7.50(1H, t, J=7.5 Hz), 7.66–7.74(6H, m), 7.92(1H, s), 8.56(1H, d, J=4.8 Hz).

IR(KBr): 1642 cm^{-1}.

mp: 204.4–206.5° C.

EXAMPLE 202

Synthesis of 6-benzenesulfonylaminomethyl-1-(2-chlorobenzyl)-2-methylbenzimidazole (264)

To a solution of 0.667 g of benzenesulfonic acid amide in 5 ml of N,N-dimethylformamide were added 0.127 g of 60% sodium hydride at room temperature, and the mixture was stirred for 1 hour. Further, 0.648 g of 1-(2-chlorobenzyl)-6-chloromethyl-2-methylbenzimidazole hydrochloride were added thereto, and the mixture was stirred at room temperature for 18 hours. Water was added to the reaction solution to stop the reaction, and the solvent was distilled off under reduced pressure. The residue was extracted with ethyl acetate and with water. The organic layer was concentrated, and was purified through silica-gel column chromatography (eluent: ethyl acetate) to give 0.240 g of 6-benzenesulfonylaminomethyl-1-(2-chlorobenzyl)-2-methylbenzimidazole (264).

Properties of Compound (264):

^{1}H-NMR(DMSO-d6, δ): 2.42(3H, s), 4.02(2H, m), 4.02 (2H, m), 5.44(2H, s), 6.36(1H, d, J=7.7 Hz), 7.03(1H, d, J=8.4 Hz), 7.18(1H, s), 7.21(1H, t), 7.33(1H, t), 7.59–7.43 (5H, m), 7.73(2H, d, J=7.5 Hz), 8.08(1H, s).

IR(KBr): 1522 cm^{-1}.

mp: 164.5–167.0° C.

EXAMPLE 203

Synthesis of 1-(biphenyl-4-ylmethyl)-2-methyl-6-[(2-pyridylmethyl)aminomethyl]benzimidazole (265)

2-Aminomethylpyridine (0.372 g) was added to a solution of 0.597 g of 1-(biphenyl-4-ylmethyl)-6-chloromethyl-2-methylbenzimidazole and 0.350 g of potassium carbonate in 3 ml of N,N-dimethylformamide, and the mixture was stirred at 60° C. for 2 hours. The reaction mixture was extracted with water and with ethyl acetate. The organic layer was washed twice with water, and the solvent was distilled off under reduced pressure. The resulting residue was purified through silica-gel column chromatography (eluent: a mixture of chloroform and methanol at a ratio of 9:1), and was recrystallized from a mixed solvent of ethyl acetate and hexane to give 0.300 g of 1-(biphenyl-4-ylmethyl)-2-methyl-6-[2-pyridylmethyl)aminomethyl] benzimidazole (265).

Properties of Compound (265):

^{1}H-NMR($CDCl_3$, δ): 2.57(3H, s), 3.91(2H, s), 3.93(2H, s), 5.35(2H, s), 7.08–7.14(3H, m), 7.23(2H, d, J=7.3 Hz), 7.30–7.35(2H, m), 7.41(2H, t), 7.50–7.55(4H, m), 7.57(1H, dt, J=1.8 and 7.6 Hz), 7.68(1H, d, J=8.1 Hz), 8.53(1H, d, J=4.9 Hz).

IR(KBr): 1618 cm^{-1}.

mp: 104.5–106.0° C.

EXAMPLE 204

Synthesis of N-benzenesulfonyl-3-[1-(2-chlorobenzyl)-2-methylbenzimidazole-6-yl] propionamide (266)

5% Palladium on carbon (0.500 g) was added to a solution of 0.607 g of N-benzenesulfonyl-1-(2-chlorobenzyl)-2-methylbenzimidazole-6-acrylamide in 150 ml of ethanol, and the mixture was stirred in a hydrogen atmosphere at room temperature for 43 hours. The solid material was separated through filtration, and the filtrate was concentrated. The residue was dissolved in a mixed solution of a 20% potassium hydrogencarbonate aqueous solution and methanol, and was adjusted to a pH of from 5 to 6 with 10% hydrochloric acid. The crystals precipitated were separated through filtration, and was dried to give 0.250 g of N-benzenesulfonyl-3-[1-(2-chlorobenzyl)-2-methylbenzimidazol-6-yl]propionamide (266).

Properties of Compound (266):

^{1}H-NMR(DMSO-d6, δ): 2.45(3H, s), 2.52(2H, t), 2.78 (2H, t), 5.37(2H, s), 6.88(1H, d, J=8.4 Hz), 7.08(2H, d, J=7.4 Hz), 7.22–7.34(3H, m), 7.36(1H, t, J=8.1 Hz), 7.55(2H, t), 7.67(1H, t), 7.84(2H, d, J=7.6 Hz), 12.04(1H, br s).

IR(KBr): 1715 cm^{-1}.

Mass(FAB): m/e 468(M+1).

mp: 229.8–233.0° C.

EXAMPLE 205

Synthesis of 6-benzenesulfonylcarbamoyl-2-methyl-1-[4-(1,2,3-thiadiazol-4-yl)benzyl]benzimidazole (267)

In the same manner as in Example 183, 0.279 g of 6-benzenesulfonylcarbamoyl-2-methyl-1-[4-(1,2,3-thiadiazol-4-yl)benzyl]benzimidazole (267) were formed from 0.382 g of N-benzenesulfonyl-4-acetylamino-3-[4-(1,2,3-thiadiazol-4-yl)benzylamino]benzamide.

Properties of Compound (267):

^{1}H-NMR(DMSO-d6, δ): 2.56(3H, s), 5.62(2H, s), 7.28 (2H, d, J=8.2 Hz), 7.58–7.63(3H, m), 7.67(1H, t, J=7.3 Hz), 7.74(1H, dd, J=8.5 and 1.2 Hz), 7.99(2H, dd, J=8.4 and 1.2 Hz), 8.10(2H, d, J=8.2 Hz), 8.19(1H, s), 9.58(1H, s), 12.47 (1H, s).

IR(KBr): 1617, 1556 cm^{-1}.

mp: 258.5–260.0° C.(decomp.).

EXAMPLE 206

Synthesis of 1-(2-chlorobenzyl)-2-methyl-6-(8-quinolinesulfonylcarbamoyl)benzimidazole sodium salt (268)

In the same manner as in Example 141, 0.400 g of 1-(2-chlorobenzyl)-2-methyl-6-(8-quinolinesulfonylcarbamoyl)benzimidazole sodium salt (268) were formed from 0.450 g of 6-carboxy-1-(2-

chlorobenzyl)-2-methylbenzimidazole, 0.485 g of N,N'-carbonyldiimidazole, 0.625 g of 8-quinolinesulfonamide and 0.457 g of diazabicycloundecene.

Properties of Compound (268):

^{1}H-NMR(DMSO-d6, δ): 2.42(3H, s), 5.48(2H, s), 6.32 (1H, d, J=7.7 Hz), 7.17(1H, t, J=7.5 Hz), 7.30(1H, t, J=7.7 Hz), 7.42(1H, d, J=8.4 Hz), 7.48(1H, dd, J=4.2 and 8.2 Hz), 7.53(1H, d, J=8.0 Hz), 7.64(1H, t, J=7.7 Hz), 7.79(1H, d, J=8.5 Hz), 7.88(1H, s), 8.04(1H, d, J=8.1 Hz), 8.33–8.37 (2H, m), 8.85(1H, dd)..

IR(KBr): 1594 cm^{-1}.

Mass(FAB): m/e 513(M+1).

mp: 348–352° C. (decomp.).

EXAMPLE 207

Synthesis of 6-(4-tert-butylbenzenesulfonylcarbamoyl)-1-(2-chlorobenzyl)-2-methylbenzimidazole sodium salt (269)

In the same manner as in Example 141, 0.280 g of 6-(4-tert-butylbenzenesulfonylcarbamoyl)-1-(2-chlorobenzyl)-2-methylbenzimidazole sodium salt (269) were obtained from 0.450 g of 6 -carboxy-1-(2-chlorobenzyl)-2-methylbenzimidazole, 0.486 g of N,N'-carbonyldiimidazole, 0.640 g of 2-tert-benzenesulfonamide and 0.657 g of diazabicycloundecene.

Properties of Compound (269):

^{1}H-NMR(DMSO-d6, δ) 1.25(9H, s), 2.46(3H, s), 5.51 (2H, s), 6.37(1H, d, J=7.7 Hz), 7.18(1H, t), 7.31(1H, t), 7.34(2H, d, J=8.4 Hz), 7.44(1H, d, J=8.4 Hz), 7.54(1H, d, J=8.0 Hz), 7.69(2H, d, J=8.5 Hz), 7.78–7.82(2H, m).

IR(KBr): 1596 cm^{-1}.

Mass(FAB): m/e 518(M+1).

mp: 359.5–362° C.

EXAMPLE 208

Synthesis of 6-benzenesulfonylcarbamoyl-2-methyl-1-[4-(trifluoromethyl)benzyl]benzimidazole (270)

In the same manner as in Production Example 32, 0.30 g of crude N-benzenesulfonyl-4-acetylamino-3-[4-(trifluoromethyl)benzylamino]benzamide were obtained from 0.50 g of N-benzenesulfonyl-4-acetylamino-3-aminobenzamide and 0.418 g of 4-(trifluoromethyl)benzyl bromide. When this crude product was dissolved in methanol and was allowed to stand, the crystals were precipitated. The crystals were separated through filtration, and were dried to give 0.160 g of 6-benzenesulfonylcarbamoyl-2-methyl-1-[4-(trifluoromethyl)benzyl]benzimidazole (270).

Properties of Compound (270):

^{1}H-NMR(DMSO-d6, δ): 2.51(3H, s), 5.66(2H, s), 7.28 (2H, d, J=8.1 Hz), 7.59–7.65(3H, m), 7.67–7.75(4H, m), 7.99(2H, d, J=7.5 Hz), 8.14(1H, d, J=1.0 Hz), 12.43(1H, s).

IR(KBr): 1618, 1550 cm^{-1}.

mp: 278.5–280.0° C.

EXAMPLE 209

Synthesis of 2-benzyl-6-carboxy-1-methylbenzimidazole hydrochloride (271)

A 5% sodium hydroxide aqueous solution (2.8 g) was added to a solution of 0.340 g of 2-benzyl-6-ethoxycarbonyl-1 -methylbenzimidazole in 4 ml of ethanol, and the mixture was heat-refluxed for 1.5 hours. The reaction mixture was acidified with 1-N hydrochloric acid, and was concentrated under reduced pressure. Ethanol was added to the residue to extract the organic substance. Ethanol was distilled off under reduced pressure to give 0.300 g of 2-benzyl-6-carboxy-1-methylbenzimidazole hydrochloride (271).

Properties of Compound (271):

^{1}H-NMR(DMSO-d6, δ): 4.00(3H, s), 4.62(2H, s), 7.33 (1H, m), 7.35–7.45(4H, m), 7.83(1H, d, J=8.4 Hz), 8.06(1H, d, J=8.4 Hz), 8.42(1H, s), 13.3(1H, br s).

EXAMPLE 210

Synthesis of 5-benzenesulfonylcarbamoyl-2-methylbenzimidazole (272)

A mixture of 0.500 g of N-benzenesulfonyl-4-acetylamino-3-aminobenzamide, 3.9 g of 35% hydrochloric acid, 15 ml of methanol and 12 ml of water was stirred at 60° C. for 1 hour. The reaction mixture was neutralized with a potassium hydrogencarbonate aqueous solution. The crystals precipitated were separated through filtration, and were dried to give 0.404 g of 5-benzenesulfonylcarbamoyl-2-methylbenzimidazole (272).

Properties of Compound (272):

^{1}H-NMR(DMSO-d6, δ): 2.79(3H, s), 7.64–7.68(2H, m), 7.72–7.76(1H, m), 7.81(1H d, J=8.7 Hz), 7.94(1H, dd, J=1.6 and 8.7 Hz), 8.02–8.05(2H, m), 8.30(1H, s).

IR(KBr): 1701 cm^{-1}.

mp: 223.0–227.5° C.

PRODUCTION EXAMPLE 45

Production of ethyl 3-methoxyacetylamino-4-nitrobenzoate

Ethyl 3-methoxyacetylamino-4-nitrobenzoate (18.7 g) was obtained from 15.0 g of ethyl 3-amino-4-nitrobenzoate and 15.0 g of methoxyacetyl chloride in the same manner as in Production Example 12.

Properties of the compound:

^{1}H-NMR($CDCl_3$, δ): 1.42(3H, t, J=7.2 Hz), 3.58(3H, s), 4.11(2H, s), 4.43(2H, q, J=7.2 Hz), 7.85(1H, dd, J=1.6 and 8.7 Hz), 8.27(1H, d, J=8.7 Hz), 9.44(1H, d, J=1.6 Hz), 11.15(1H, s).

EXAMPLE 211

Synthesis of 1-(biphenyl-4-ylmethyl)-6-ethoxycarbonyl-2-methoxymethylbenzimidazole (273)

Crude ethyl 3-[N-(biphenyl-4-ylmethyl) methoxyacetylamino]-4-nitrobenzoate (2.02 g) was obtained from 2.00 g of ethyl 3-methoxyacetylamino-4-nitrobenzoate and 2.98 g of 4-biphenylmethyl bromide in the same manner as in Production Example 14. Subsequently, 1.44 g of crude 1-(biphenyl-4-ylmethyl)-6-ethoxycarbonyl-2-methoxymethylbenzimidazole (273) were obtained in the same manner as in Example 24.

EXAMPLE 212

Synthesis of 1-(biphenyl-4-ylmethyl)-6-carboxy-2-methoxymethylbenzimidazole (274)

In the same manner as in Example 53, 0.864 g of 1-(biphenyl-4-ylmethyl)-6-carboxy-2-

methoxymethylbenzimidazole (274) were formed from 1.44 g of crude 1-(biphenyl-4-ylmethyl)-6-ethoxycarbonyl-2-methoxymethylbenzimidazole.

Properties of Compound (274):

^{1}H-NMR(DMSO-d6, δ): 3.35(3H, s), 4.77(2H, s), 5.68 (2H, s), 7.25(2H, d, J=8.3 Hz), 7.35(1H, t, J=7.4 Hz), 7.44(2H, t, J=7.5 Hz), 7.61–7.66(4H, m), 7.74(1H, d, J=8.6 Hz), 7.83(1H, dd, J=1.6 and 8.5 Hz), 8.08(1H, d, J=1.2 Hz), 12.83(1H, s).

EXAMPLE 213

Synthesis of 1-(biphenyl-4-ylmethyl)-6-(1-butanesulfonylcarbamoyl)-2-methoxymethylbenzimidazole (275)

In the same manner as in Example 98, 0.429 g of 1-(biphenyl-4-ylmethyl)-6-(1-butanesulfonylcarbamoyl)-2-methoxymethylbenzimidazole (275) were formed from 0.400 g of 1-(biphenyl-4-ylmethyl)-6-carboxy-2-methoxymethylbenzimidazole, 0.348 g of N,N'-carbonyldiimidazole, 0.294 g of 1-butanesulfonamide and 0.327 g of diazabicycloundecene.

Properties of Compound (275):

^{1}H-NMR(DMSO-d6, δ): 0.84(3H, t, J=7.4 Hz), 1.35–1.42 (2H, m), 1.62–1.70(2H, m), 3.33(3H, s), 3.51(2H, t, J=7.6 Hz), 4.74(2H, s), 5.65(2H, s), 7.26(2H, d, J=8.3 Hz), 7.35 (1H, t, J=7.3 Hz), 7.44(2H, t, J=7.5 Hz), 7.62–7.67(4H, m), 7.78(1H, d, J=8.6 Hz), 7.84(1H, dd, J=1.5 and 8.4 Hz), 8.24(1H, d, J=1.5 Hz), 12.01(1H, s).

IR(KBr): 1684 cm^{-1}.

mp: 176.0–178.5° C.

EXAMPLE 214

Synthesis of 1-(4-benzyloxybenzyl)-6-ethoxycarbonyl-2-methoxymethylbenzimidazole (276)

Crude ethyl 3-[N-4-benzyloxybenzyl) methoxyacetylamino]-4-nitrobenzoate (2.14 g) was obtained from 2.00 g of ethyl 3-methoxyacetylamino-4-nitrobenzoate and 3.30 g of 4-benzyloxybenzyl chloride in the same manner as in Production Example 14. Subsequently, 1.66 g of crude 1-(4-benzyloxybenzyl)-6-ethoxycarbonyl-2-methoxymethylbenzimidazole (276) were obtained in the same manner as in Example 24.

EXAMPLE 215

Synthesis of 1-(4-benzyloxybenzyl)-6-carboxy-2-methoxymethylbenzimidazole (277)

In the same manner as in Example 53, 2.64 g of 1-(4-benzyloxybenzyl)-6-carboxy-2-methoxymethylbenzimidazole (277) were formed from 3.75 g of crude 1-(4-benzyloxybenzyl)-6-ethoxycarbonyl-2-methoxymethylbenzimidazole.

Properties of Compound (277):

^{1}H-NMR(DMSO-d6, δ): 3.34(3H, s), 4.74(2H, s), 5.05 (2H, s), 5.53(2H, s), 6.97(2H, d, J=8.7 Hz), 7.15(2H, d, J=8.7 Hz), 7.31(1H, t, J=7.2 Hz), 7.41(2H, d, J=7.2 Hz), 7.71(1H, d, J=8.4 Hz), 7.81(1H, dd, J=1.5 and 7.4 Hz), 8.04(1H, d, J=1.1 Hz), 12.81(1H, s).

EXAMPLE 216

Synthesis of 1-(4-benzyloxybenzyl)-6-(1-butanesulfonylcarbamoyl)-2-methoxymethylbenzimidazole (278)

In the same manner as in Example 155, 0.321 g of 1-(4-benzyloxybenzyl)-6-(1-butanesulfonylcarbamoyl)-2-methoxymethylbenzimidazole (278) were formed from 0.400 g of 1-(4-benzyloxybenzyl)-6-carboxy-2-methoxymethylbenzimidazole, 0.322 g of N,N'-carbonyldiimidazole, 0.272 g of 1-butanesulfonamide and 0.302 g of diazabicycloundecene.

Properties of Compound (278):

^{1}H-NMR(DMSO-d6, δ): 0.86(3H, t, J=7.4 Hz), 1.37–1.44 (2H, m),1.65–1.71(2H, m), 3.32(3H, s), 3.52(2H, t, J=7.6 Hz), 4.71(2H, s), 5.05(2H, s), 5.51(2H, s), 6.98(2H, d, J=8.7 Hz), 7.15(2H, d, J=8.3 Hz), 7.31(1H, t, J=7.2 Hz), 7.37(2H, t, J=7.2 Hz), 7.41(2H, d, J=7.1 Hz), 7.74(1H, d, J=8.5 Hz), 7.82(1H, dd, J=1.5 and 8.5 Hz), 8.21(1H, s), 11.98(1H, s).

IR(KBr): 1685 cm^{-1}.

mp: 72.0–74.0° C.

EXAMPLE 217

Synthesis of 1-(2,4-dichlorobenzyl)-6-ethoxycarbonyl-2-methoxymethylbenzimidazole (279)

Crude ethyl 3-[N-2,4-dichlorobenzyl) methoxyacetylamino]-4-nitrobenzoate was obtained from 2.00 g of ethyl 3-methoxyacetylamino-4-nitrobenzoate and 2.08 g of 2,4-dichlorobenzyl chloride in the same manner as in Production Example 14. Subsequently, 3.15 g of crude 1-(2,4-dichlorobenzyl)-6-ethoxycarbonyl-2-methoxymethylbenzimidazole (279) were obtained in the same manner as in Example 24.

EXAMPLE 218

Synthesis of 6-carboxy-1-(2,4-dichlorobenzyl)-2-methoxymethylbenzimidazole (280)

In the same manner as in Example 53, 1.46 g of 6-carboxy-1-(2,4-dichlorobenzyl)-2-methoxymethylbenzimidazole (280) were formed from 3.15 g of crude 1-(2,4-dichlorobenzyl)-6-ethoxycarbonyl-2-methoxymethylbenzimidazole.

Properties of Compound (280):

^{1}H-NMR(DMSO-d6, δ): 3.23(3H, s), 4.70(2H, s), 5.68 (2H, s), 6.54(1H, d, J=8.5 Hz), 7.31(1H, dd, J=2.2 and 8.5 Hz), 7.73(1H, d, J=2.1 Hz), 7.76(1H, d, J=8.5 Hz), 7.86(1H, dd, J=1.5 and 8.5 Hz), 8.00(1H, d, J=1.1 Hz), 12.85(1H, s).

EXAMPLE 219

Synthesis of 6-(1-butanesulfonylcarbamoyl)-1-(2,4-dichlorobenzyl)- 2-methoxymethylbenzimidazole (281)

In the same manner as in Example 98, 0.430 g of 6-(1-butanesulfonylcarbamoyl)-1-(2,4-dichlorobenzyl)-2-methoxymethylbenzimidazole (281) were formed from 0.400 g of 6-carboxy-1-(2,4-dichlorobenzyl)-2-methoxymethylbenzimidazole, 0.355 g of N,N'-carbonyldiimidazole, 0.300 g of 1-butanesulfonamide and 0.333 g of diazabicycloundecene.

Properties of Compound (281):

^{1}H-NMR(DMSO-d6, δ): 0.85(3H, t, J=7.3 Hz), 1.37–1.42 (2H, m), 1.63–1.69(2H, m), 3.21(3H, s), 3.51(2H, t, J=7.6 Hz), 4.68(2H, s), 5.65(2H, s), 6.46(1H, d, J=8.5 Hz), 7.31 (1H, dd, J=2.0 and 8.4 Hz), 7.75(1H, d, J=2.1 Hz), 7.80(1H, d, J=8.5 Hz), 7.86(1H, dd, J=1.7 and 8.6 Hz), 8.14(1H, d, J=1.2 Hz), 12.00(1H, s).

IR(KBr): 1694 cm^{-1}.

mp: 168.5–170.5° C.

EXAMPLE 220

Synthesis of 1-(2-chlorobenzyl)-2-methyl-6-(1-propanesulfonylcarbamoyl)benzimidazole (282)

In the same manner as in Example 98, 0.459 g of 1-(2-chlorobenzyl)-2-methyl-6-(1-propanesulfonylcarbamoyl)benzimidazole (282) were formed from 0.400 g of 6-carboxy-1-(2-chlorobenzyl)-2-methylbenzimidazole, 0.431 g of N,N'-carbonyldiimidazole, 0.328 g of 1-propanesulfonamide and 0.404 g of diazabicycloundecene.

Properties of Compound (282):

^{1}H-NMR(DMSO-d6, δ): 0.98(3H, t, J=7.4 Hz), 1.67–1.75 (2H, m), 2.50(3H, s), 3.49(2H, t, J=7.7 Hz), 5.61(2H, s), 6.45(1H, d, J=7.0 Hz), 7.24(1H, dt, J=0.8 and 7.8 Hz), 7.35(1H, dt, J=1.4 and 7.4 Hz), 7.63(1H, dd, J=0.9 and 7.9 Hz), 7.69(1H, d, J=8.5 Hz), 7.81(1H, dd, J=1.6 and 8.5 Hz), 8.12(1H, d, J=1.6 Hz), 11.90(1H, s).

IR(KBr): 1676 cm^{-1}.

mp: 217.5–218.5° C.

EXAMPLE 221

Synthesis of 6-ethanesulfonylcarbamoyl-1-(2-chlorobenzyl)-2 -methylbenzimidazole (283)

In the same manner as in Example 98, 0.459 g of 6-ethanesulfonylcarbamoyl-1-(2-chlorobenzyl)-2-methylbenzimidazole (283) were formed from 0.400 g of 6-carboxy-1-(2-chlorobenzyl)-2-methylbenzimidazole, 0.431 g of N,N'-carbonyldiimidazole, 0.290 g of ethanesulfonamide and 0.404 g of diazabicycloundecene.

Properties of Compound (283):

^{1}H-NMR(DMSO-d6, δ): 1.23(3H, t, J=7.3 Hz), 2.50(3H, s), 3.50(2H, q, J=7.3 Hz), 5.61(2H, s), 6.45(1H, d, J=6.7 Hz), 7.24(1H, dt, J=0.9 and 7.5 Hz), 7.35(1H, dt, J=1.4 and 7.5 Hz), 7.58(1H, dd, J=1.0 and 8.0 Hz), 7.69(1H, d, J=8.5 Hz), 7.81(1H, dd, J=1.6 and 8.4 Hz), 8.13(1H, d, J=1.5 Hz), 11.86(1H, s).

IR(KBr): 1673 cm^{-1}.

mp: 256.5–258.5° C.

EXAMPLE 222

Synthesis of 6-(propanesultam-1-ylcarbonyl)-1-(2-chlorobenzyl)-2-methylbenzimidazole (284)

In the same manner as in Example 98, 0.323 g of 6-(propanesultam-1-ylcarbonyl)-1-(2-chlorobenzyl)-2-methylbenzimidazole (284) were formed from 0.400 g of 6-carboxy-1-(2-chlorobenzyl)-2-methylbenzimidazole, 0.431 g of N,N'-carbonyldiimidazole, 0.420 g of 1-(3-chloropropane)sulfonamide and 0.404 g of diazabicycloundecene.

Properties of Compound (284):

^{1}H-NMR(DMSO-d6, δ): 2.27–2.33(2H, m), 2.52(3H, s), 3.52(2H, t, J=7.0 Hz), 3.87(2H, t, J=6.6 Hz), 5.59(2H, s), 6.57(1H, d, J=7.7 Hz), 7.23(1H, t, J=7.6 Hz), 7.34(1H, t, J=6.4 Hz), 7.53–7.58(2H, m), 7.67(1H, d, J=8.4 Hz), 7.79 (1H, d, J=l.1Hz).

IR(KBr): 1648 cm^{-1}.

mp: 165.5–166.6° C.

EXAMPLE 223

Synthesis of 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-cyclopropylbenzimidazole potassium salt (285)

In the same manner as in Example 170, 0.196 g of 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-cyclopropylbenzimidazole potassium salt (285) were obtained from 0.400 g of N-benzenesulfonyl-4-amino-3-(biphenyl-4-ylmethylamino)benzamide and 0.101 g of cyclopropanecarbonyl chloride via N-benzenesulfonyl-3-(biphenyl-4-ylmethylamino)-4-cyclopropanecarbonylaminobenzamide.

Properties of Compound (285):

^{1}H-NMR(DMSO-d6, δ):1.00–1.15(4H, m), 2.23–2.31 (1H, m), 5.66(2H, s), 7.21(2H, m, J=9.1 Hz), 7.32–7.45(7H, m), 7.59–7.63(4H, m), 7.78–7.83(3H, m), 7.97(1H, s).

IR(Nujol): 1540 cm^{-1}.

Mass(FAB): m/e 546(M+1).

mp: 220.8–224.8° C.

EXAMPLE 224

Synthesis of 1-(2-chlorobenzyl)-2-methyl-6-(1-pentanesulfonylcarbamoyl)benzimidazole (286)

In the same manner as in Example 98, 0.491 g of 1-(2-chlorobenzyl)-2-methyl-6-(1-pentanesulfonylcarbamoyl)benzimidazole (286) were formed from 0.400 g of 6-carboxy-1-(2-chlorobenzyl)-2-methylbenzimidazole, 0.431 g of N,N'-carbonyldiimidazole, 0.402 g of 1-pentanesulfonamide and 0.404 g of diazabicycloundecene.

Properties of Compound (286):

^{1}H-NMR(DMSO-d6, δ): 0.81(3H, t, J=7.2 Hz), 1.23–1.28 (2H, m), 1.32–1.37(2H, m), 1.65–1.69(2H, m), 3.50(2H, t, J=7.8 Hz), 5.61(2H, s), 6.45(1H, d, J=7.5 Hz), 7.24(1H, t, J=7.6 Hz), 7.35(1H, t, J=7.5 Hz), 7.57(1H, d, J=7.9 Hz), 7.69(1H, d, J=8.5 Hz), 7.81(1H, dd, J=1.7 and 8.4 Hz), 8.12(1H, d, J=1.2 Hz), 12.25(1H, s).

IR(KBr): 1684 cm^{-1}.

mp: 173.3–179.8° C.

EXAMPLE 225

Synthesis of 1-(2-chlorobenzyl)-2-methyl-6-[(3-methylbutane)sulfonylcarbamoyl]benzimidazole (287)

In the same manner as in Example 98, 0.284 g of 1-(2-chlorobenzyl)-2-methyl-6-[(3-methylbutane) sulfonylcarbamoyl]benzimidazole (287) were formed from 0.300 g of 6-carboxy-1-(2 -chlorobenzyl)-2-methylbenzimidazole, 0.323 g of N,N-carbonyldiimidazole, 0.302 g of 1-(3-methyl)butanesulfonamide and 0.303 g of diazabicycloundecene.

Properties of Compound (287):

^{1}H-NMR(DMSO-d6, δ): 0.84(6H, d, J=6.5 Hz), 1.52–1.59(2H, m), 1.61–1.70(1H, m), 3.44(2H, t, J=7.9 Hz), 5.60(2H, s), 6.45(1H, d, J=7.8 Hz), 7.24(1H, t, J=7.6 Hz), 7.35(1H, t, J=7.4 Hz), 7.57(1H, d, J=7.9 Hz), 7.66(1H, d, J=8.5 Hz), 7.81(1H, dd, J=1.6 and 8.6 Hz), 8.09(1H, s), 11.87(1H, s).

IR(KBr): 1682 cm^{-1}.

mp: 201.0–204.1° C.

EXAMPLE 226

Synthesis of 1-(2-chlorobenzyl)-6-(1-hexanesulfonylcarbamoyl)-2-methylbenzimidazole (288)

In the same manner as in Example 98, 0.379 g of 1-(2-chlorobenzyl)-6-(1-hexanesulfonylcarbamoyl)-2-

methylbenzimidazole (288) were formed from 0.300 g of 6-carboxy-1-(2-chlorobenzyl)-2-methylbenzimidazole, 0.323 g of N,N-carbonyldiimidazole, 0.335 g of 1-hexanesulfonamide and 0.303 g of diazabicycloundecene.

Properties of Compound (288):

^{1}H-NMR(DMSO-d6, δ): 0.81(3H, t, J=7.0 Hz), 1.18–1.28 (4H, m), 1.32–1.41(2H, m), 1.63–1.71(2H, m), 2.53(3H, s), 3.50(2H, t, J=7.7 Hz), 5.64(2H, s), 6.51(1H, d, J=7.7 Hz), 7.25(1H, dt, J=1.2 and 7.8 Hz), 7.36(1H, dt, J=1.4 and 7.7 Hz), 7.58(1H, dd, J=1.0 and 8.0 Hz), 7.72(1H, d, J=8.5 Hz), 7.84(1H, dd, J=1.6 and 8.5 Hz), 8.15(1H, d, J=1.3 Hz), 11.87(1H, s).

IR(KBr): 1682 cm^{-1}.

mp: 141.2–143.5° C.

EXAMPLE 227

Synthesis of 6-tert-butoxycarbonylamino-1-(2-chlorobenzyl)-2-methylbenzimidazole (289)

In the same manner as in Example 18, 0.760 g of 6-tert-butoxycarbonylamino-1-(2-chlorobenzyl)-2-methylbenzimidazole (289) were formed from 1.01 g of 6-carboxy-1-(2-chlorobenzyl)-2 -methylbenzimidazole, 1 ml of diphenylphosphorylazide, 1 ml of diisopropylethylamine and 25 ml of tert-butyl alcohol.

Properties of Compound (289):

^{1}H-NMR($CDCl_3$, δ): 1.49(9H, S), 2.47(3H, s), 5.37(2H, s), 6.41(1H, d, J=7.5 Hz), 6.55(1H, br s), 6.93(1H, dd, J=1.9 and 8.6 Hz), 7.08(1H, t, J=7.5 Hz), 7.22(1H, t), 7.44(1H, d, J=8.0 Hz), 7.62(2H, d, J=8.6 Hz).

EXAMPLE 228

Synthesis of 6-amino-1-(2-chlorobenzyl)-2-methylbenzimidazole (290)

In the same manner as in Example 22, 0.420 g of 6-amino-1-(2-chlorobenzyl)-2-methylbenzimidazole (290) were formed from 0.760 g of 6-tert-butoxycarbonylamino-1-(2-chlorobenzyl)-2-methylbenzimidazole.

Properties of Compound (290):

^{1}H-NMR(DMSO-d6, δ): 2.37(3H, s), 4.83(2H, br s), 5.32(2H, s), 6.33(1H, d, J=1.9 Hz), 6.42(1H, d, J=7.7 Hz), 6.46(1H, dd, J=1.9 and 8.5 Hz), 7.19–7.24(2H, m), 7.31(1H, t), 7.53(1H, d, J=7.9 Hz).

EXAMPLE 229

Synthesis of 6-(1-butanesulfonylamino)-1-(2-chlorobenzyl)-2-methylbenzimidazole (291)

In the same manner as in Example 20, 0.230 g of 6-(1-butanesulfonylamino)-1-(2-chlorobenzyl)-2-methylbenzimidazole (291) were formed from 0.300 g of 6-amino-1-(2-chlorobenzyl)-2-methylbenzimidazole, 0.216 g of 1-butanesulfonyl chloride and 0.130 g of triethylamine.

Properties of Compound (291):

^{1}H-NMR(DMSO-d6, δ): 0.74(3H, m), 1.23(2H, m), 1.55 (2H, m), 2.50(3H, s), 2.89(2H, m), 5.47(2H, s), 6.58(1H, d, J=7.4 Hz). 7.02(1H, d, J=8.5 Hz), 7.10(1H, s), 7.23(1H, t), 7.33(1H, t), 7.52(2H, m), 9.55(1H, s).

IR(KBr): 1629 cm^{-1}.

mp: 149.5–151.0° C.

PRODUCTION EXAMPLE 46

Production of methyl 2-[N-(2,4-dichlorobenzyl) acetylamino]-3 -nitrobenzoate

In the same manner as in Production Example 14, 0.250 g of methyl 2-[N-(2,4-dichlorobenzyl)acetylamino]-3-nitrobenzoate were formed from 1.00 g of methyl 2-acetylamino-3-nitrobenzoate and 0.985 g of 2,4-dichlorobenzyl chloride.

Properties of the compound:

^{1}H-NMR($CDCl_3$, δ): 1.99(3H, s), 3.71(3H, s), 4.85(1H, d, J=4.5 Hz), 4.98(1H, d, J=4.5 Hz), 7.17–7.22(2H, m), 7.46 (1H, d, J=7.9 Hz), 7.63(1H, t, J=7.9 Hz), 7.98(1H, d, J=8.0 Hz), 8.09(1H, d, J=7.9 Hz).

EXAMPLE 230

Synthesis of 1-(2,4-dichlorobenzyl)-7-ethoxycarbonyl-2-methylbenzimidazole (292)

In the same manner as in Example 24, 5.15 g of 1-(2,4-dichlorobenzyl)-7-ethoxycarbonyl-2-methylbenzimidazole (292) were formed from 6.50 g of methyl 2-[N-(2,4-dichlorobenzyl)acetylamino]-3-nitrobenzoate.

Properties of Compound (292):

^{1}H-NMR($CDCl_3$, δ): 2.53(3H, s), 3.70(3H, s), 5.72(2H, s), 6.26(1H, d, J=8.4 Hz), 7.04(1H, dd, J=2.0 and 8.4 Hz), 7.28(1H, t, J=7.9 Hz), 7.45(1H, d, J=2.0 Hz), 7.75(1H, d, J=7.8 Hz), 7.93(1H, d, J=7.9 Hz).

EXAMPLE 231

Synthesis of 7-carboxy-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole (293)

In the same manner as in Example 53, 1.76 g of 7-carboxy-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole (293) were formed from 2.00 g of 1-(2,4-dichlorobenzyl)-7-ethoxycarbonyl-2-methylbenzimidazole.

Properties of Compound (293):

^{1}H-NMR(DMSO-d6, δ): 2.49(3H, s), 5.81(2H, s), 6.09 (1H, d, J=8.4 Hz), 7.21–7.28(2H, m), 7.62(1H, d, J=7.8 Hz), 7.67(1H, d, J=2.2 Hz), 7.83(1H, d, J=8.0 Hz), 13.04(1H, br s).

EXAMPLE 232

Synthesis of 7-(1-butanesulfonylcarbamoyl)-1-(2,4-dichlorobenzyl)- 2-methylbenzimidazole (294)

In the same manner as in Example 98, 0.325 g of 7-(1-butanesulfonylcarbamoyl)-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole (294) were formed from 0.463 g of 7-carboxy-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole, 0.448 g of N,N'-carbonyldiimidazole, 0.379 g of 1-butanesulfonamide and 0.421 g of diazabicycloundecene.

Properties of Compound (294):

^{1}H-NMR(DMSO-d6, δ): 0.84(3H, t, J=7.3 Hz), 1.33(2H, m), 1.44(2H, m), 2.53(3H, s), 3.16(2H, m), 5.64(2H, s), 6.03(1H, d, J=8.4 Hz), 7.25(1H, dd, J=2.1 and 8.4 Hz), 7.30(1H, t, J=7.8 Hz), 7.44(1H, d, J=7.4 Hz), 7.68(1H, d, J=2.1 Hz), 7.87(1H, d, J=7.8 Hz), 12.18(1H, br s).

IR(KBr): 1690 cm^{-1}.

mp: 98.5–102.0° C.

EXAMPLE 233

Synthesis of 1-(2-chlorobenzyl)-2-methyl-6-[1-[3-(trimethylsilyl)propane]sulfonylcarbamoyl] benzimidazole (295)

In the same manner as in Example 149, 0.604 g of 1-(2-chlorobenzyl)-2-methyl-6-[1-[3-(trimethylsilyl) propane]sulfonylcarbamoyl]benzimidazole (295) were

formed from 0.400 g of 6-carboxy-1-(2-chlorobenzyl)-2-methylbenzimidazole, 0.431 g of N,N'-carbonyldiimidazole, 0.520 g of 1-[3-(trimethylsilyl)propane]sulfonamide and 0.404 g of diazabicycloundecene.

Properties of Compound (295):

^{1}H-NMR(DMSO-d6, δ): −0.06(9H, s), 0.61(2H, t, J=8.6 Hz), 1.66–1.73(2H, m), 2.50(3H, s), 3.51(2H, t, J=7.7 Hz), 5.61(2H, s), 6.46(1H, d, J=7.8 Hz), 7.24(1H, t, J=7.6 Hz), 7.35(1H, t, J=7.6 Hz), 7.57(1H, dd, J=7.9 and 0.9 Hz), 7.70(1H, d, J=8.5 Hz), 7.81(1H, dd, J=1.5 and 8.5 Hz), 8.12(1H, d, J=1.4 Hz), 11.98(1H, s).

IR(KBr): 1688 cm^{-1}.

mp: 197.0–203.9° C.

EXAMPLE 234

Synthesis of 4-ethoxycarbonyl-2-methylbenzimidazole (296)

A mixture of 8.03 g of methyl 2-acetylamino-3-nitrobenzoate, 18.8 g of reduced iron, 20 ml of acetic acid and 40 ml of ethanol was heat-refluxed for 18 hours. After the solvent was concentrated, chloroform and 10% hydrochloric acid were added to the residue for extraction. The aqueous layer was acidified with a saturated aqueous solution of sodium hydrogencarbonate, and was extracted with chloroform. Chloroform was then distilled off under reduced pressure to give 1.61 g of 4-ethoxycarbonyl-2-methylbenzimidazole (296).

Properties of Compound (296):

^{1}H-NMR($CDCl_3$, δ): 1.43(3H, t), 2.66(3H, s), 4.45(2H, q), 7.24–7.28(1H, m), 7.84–7.89(2H, m), 10.26(1H, br s).

EXAMPLE 235

Synthesis of 1-(2,4-dichlorobenzyl)-4-ethoxycarbonyl-2-methylbenzimidazole (297)

A mixture of 1.61 g of 4-ethoxycarbonyl-2-methylbenzimidazole, 3.08 g of 2,4-dichlorobenzyl chloride, 1.51 g of potassium iodide, 1.05 g of potassium carbonate and 4 ml of N,N-dimethylformamide was stirred at 80° C. for 16 hours. The reaction mixture was extracted with chloroform and with water. The chloroform layer was washed with water, dried, and concentrated. The residue was purified through silica-gel column chromatography (eluent: a mixture of hexane and ethyl acetate at a ratio of 2:8) to give 0.730 g of 1-(2,4-dichlorobenzyl)-4-ethoxycarbonyl-2-methylbenzimidazole (297).

Properties of Compound (297):

^{1}H-NMR($CDCl_3$, δ): 1.47(3H, t, J=7.1 Hz), 2.63(3H, s), 4.52(2H, q, J=7.1 Hz), 5.39(2H, s), 6.30(1H, d, J=8.4 Hz), 7.06(1H, dd, J=2.1 and 8.4 Hz), 7.25(1H, t, J=7.9 Hz), 7.32(1H, dd, J=1.0 and 7.9 Hz), 7.48(1H, d, J=2.0 Hz), 7.93(1H, dd, J=1.0 and 7.7 Hz).

EXAMPLE 236

Synthesis of 4-carboxy-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole (298)

In the same manner as in Example 53, 0.575 g of 4-carboxy-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole (298) were formed from 0.730 g of 1-(2,4-dichlorobenzyl)-4-ethoxycarbonyl-2-methylbenzimidazole.

Properties of Compound (298):

^{1}H-NMR(DMSO-d6, δ): 2.65(3H, s), 5.67(2H, s), 6.73 (1H, d, J=8.3 Hz), 7.33(1H, dd, J=2.2 and 8.4 Hz), 7.39(1H, t, J=7.9 Hz), 7.74(1H, d, J=2.2 Hz), 7.76(1H, d, J=8.2 Hz), 7.85(1H, d, J=7.5 Hz).

EXAMPLE 237

Synthesis of 4-(1-butanesulfonylcarbamoyl)-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole (299)

In the same manner as in Example 98, 0.275 g of 4-(1-butanesulfonylcarbamoyl)-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole (299) were formed from 0.350 g of 4-carboxy-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole, 0.339 g of N,N'-carbonyldiimidazole, 0.287 g of 1-butanesulfonamide and 0.318 g of diazabicycloundecene.

Properties of Compound (299):

^{1}H-NMR(DMSO-d6, δ): 0.86(3H, t, J=7.3 Hz), 1.42(2H, m), 1.73(2H, m), 2.61(3H, s), 3.61(2H, m), 5.65(2H, s), 6.67(1H, d, J=8.4 Hz), 7.32(1H, dd, J=2.1 and 8.4 Hz), 7.39(1H, t, J=7.9 Hz), 7.73(1H, d, J=2.1 Hz), 7.78(1H, d, J=8.0 Hz), 7.91(1H, d, J=7.7 Hz), 12.66(1H, br s).

IR(KBr): 1699 cm^{-1}.

mp: 180.7–183.6° C.

EXAMPLE 238

Synthesis of 1-(4-benzyloxybenzyl)-6-ethoxycarbonyl-2-methylbenzimidazole (300)

In the same manner as in Production Example 14, crude ethyl 3-[N-(4-benzyloxybenzyl)acetylamino]-4-nitrobenzoate was obtained from 2.00 g of ethyl 3-acetylamino-4-nitrobenzoate and 3.69 g of 4-benzyloxybenzyl chloride. Subsequently, 4.09 g of crude 1-(4-benzyloxybenzyl)-6-ethoxycarbonyl-2-methylbenzimidazole (300) were formed in the same manner as in Example 24.

EXAMPLE 239

Synthesis of 1-(4-benzyloxybenzyl)-6-carboxy-2-methylbenzimidazole (301)

In the same manner as in Example 53, 1.13 g of 1-(4-benzyloxybenzyl)-6-carboxy-2-methylbenzimidazole (301) were formed from 4.09 g of 1-(4-benzyloxybenzyl)-6-ethoxycarbonyl-2-methylbenzimidazole.

Properties of Compound (301):

^{1}H-NMR(DMSO-d6, δ): 2.57(3H, s), 5.05(2H, s), 5.48 (2H, s), 6.97(2H, d, J=8.6 Hz), 7.08(2H, d, J=8.5 Hz), 7.28–7.43(5H, m), 7.60(1H, d, J=8.3 Hz), 7.78(1H, d, J=7.5 Hz), 8.07(1H, s), 12.72(1H, s).

EXAMPLE 240

Synthesis of 1-(4-benzyloxybenzyl)-6-(1-butanesulfonylcarbamoyl)-2-methylbenzimidazole (302)

In the same manner as in Example 149, 0.206 g of 1-(4-benzyloxybenzyl)-6-(1-butanesulfonylcarbamoyl)-2-methylbenzimidazole (302) were formed from 0.300 g of 6-carboxy-1-(4-benzyloxybenzyl)-2-methylbenzimidazole, 0.242 g of N,N'-carbonyldiimidazole, 0.204 g of 1-butanesulfonamide and 0.227 g of diazabicycloundecene.

Properties of Compound (302):

^{1}H-NMR(DMSO-d6, δ): 0.87(3H, t, J=7.3 Hz), 1.38–1.43 (2H, m), 1.64–1.71(2H, m), 2.54(3H, s), 3.49(2H, t, J=6.8 Hz), 5.05(2H, s), 5.45(2H, s), 6.98(2H, d, J=8.7 Hz), 7.10

(2H, d, J=8.7 Hz), 7.31(1H, t, J=7.2 Hz), 7.37(2H, t, J=7.2 Hz), 7.41(2H, d, J=7.3 Hz), 7.62(1H, d, J=8.5 Hz), 7.79(1H, dd, J=1.5 and 8.4 Hz), 8.23(1H, s), 11.93(1H, s).

IR(KBr): 1684 cm^{-1}.

mp: 132.4–137.7° C.

EXAMPLE 241

Synthesis of 6-ethoxycarbonyl-1-[(2'-cyanobiphenyl-4-yl)methyl]-2-methylbenzimidazole (303)

In the same manner as in Production Example 14, 0.750 g of crude ethyl 3-[N-[(2'-cyanobiphenyl-4-yl)methyl] acetylamino]-4-nitrobenzoate were obtained from 1.00 g of ethyl 3-acetylamino-4-nitrobenzoate and 1.30 g of 4'-bromomethyl-2-cyanobiphenyl. Subsequently, 0.410 g of 6-ethoxycarbonyl-1-[(2'-cyanobiphenyl- 4-yl)methyl]-2-methylbenzimicazole (303) were formed in the same manner as in Example 24.

Properties of Compound (303):

^{1}H-NMR($CDCl_3$, δ): 1.40(3H, t), 2.63(3H, s), 4.39(2H, q), 5.46(2H, s), 7.17(2H, d), 7.40–7.66(5H, m), 7.73–7.78 (2H, m), 8.00(1H, dd, J=1.5 and 8.5 Hz), 8.05(1H, d, J=1.2 Hz).

EXAMPLE 242

Synthesis of 6-carboxy-1-[(2'-cyanobiphenyl-4-yl) methyl]-2-methylbenzimidazole (304)

In the same manner as in Example 53, 0.190 g of 6-carboxy-1-[(2'-cyanobiphenyl-4-yl)methyl]-2-methylbenzimidazole (304) were formed from 0.410 g of 6-ethoxycarbonyl-1-[(2'-cyanobiphenyl-4-yl)methyl]-2-methylbenzimidazole.

Properties of Compound (304):

^{1}H-NMR(DMSO-d6, δ): 2.59(3H, s), 5.67(2H, s), 7.24 (2H, d, J=8.1 Hz), 7.53–7.64(5H, m), 7.75(1H, t, J=7.7 Hz), 7.80(1H, d), 7.92(1H, d, J=7.7 Hz), 8.12(1H, s), 12.74(1H, br s).

EXAMPLE 243

Synthesis of 6-(1-butanesulfonylcarbamoyl)-1-[(2'-cyanobiphenyl-4-yl)methyl]-2-methylbenzimidazole (305)

In the same manner as in Example 155, 0.155 g of 6-(1-butanesulfonylcarbamoyl)-1-[(2'-cyanobiphenyl-4-yl) methyl]-2-methylbenzimidazole (305) were formed from 0.187 g of 6-carboxy-1-[(2'-biphenyl-4-yl)methyl]-2-methylbenzimidazole, 0.160 g of N,N'-carbonyldiimidazole, 0.135 g of 1-butanesulfonamide and 0.150 g of diazabicycloundecene by being purified through silica-gel column chromatography (eluent: a mixture of chloroform and methanol at a ratio of 20:1).

Properties of Compound (305):

^{1}H-NMR(DMSO-d6, δ): 0.83(3H, t, J=7.4 Hz), 1.34(2H, m), 1.60(2H, m),2.56(3H, s), 3.27(2H, m), 5.62(2H, s), 7.23(2H, d, J=8.2 Hz), 7.53–7.57(4H, m), 7.60(1H, d, J=7.8 Hz), 7.75(1H, dt, J=1.0 and 7.8 Hz), 7.83(1H, dd, J=1.5 and 8.4 Hz), 7.92(1H, d), 8.13(1H, s), 11.92(1H, br s).

IR(KBr): 2223 cm^{-1}.

mp: 115–118° C.

PRODUCTION EXAMPLE 47

Production of 2-fluoro-4'-methylbiphenyl

Thirty milliliters of a 1.6-M-n-butyllithium hexane solution and a solution of 8.33 g of 4-bromotoluene in 30 ml of tetrahydrofuran were added in this order to 30 ml of tetrahydrofuran which had been cooled to −78° C. in a nitrogen atmosphere, and the mixture was then stirred at −78° C. for 1 hour. A solution containing 6.64 g of zinc chloride which had been dehydrated through heat-melting under reduced pressure in 30 ml of tetrahydrofuran was added thereto at −78° C., and the mixture was stirred at room temperature for 1 hour. This solution was added to a solution of 7.22 g of 2-fluoroiodobenzene and 0.52 g of tetrakis (trifluorophosphine)palladium (O) in 30 ml of tetrahydrofuran at room temperature, and the mixed solution was stirred for 24 hours. The reaction solution was diluted with 300 ml of ethyl acetate, and the dilute solution was extracted with the addition of 10% hydrochloric acid. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried, and then concentrated. The residue was purified through silica-gel column chromatography (eluent: hexane) to give 6.05 g of oily 2-fluoro-4'-methylbiphenyl.

Properties of the compound:

^{1}H-NMR($CDCl_3$, δ): 2.39(3H, s), 7.10–7.30(5H, m), 7.39–7.49(3H, m).

PRODUCTION EXAMPLE 48

Production of 2-fluoro-4'-bromomethylbiphenyl

A mixture of 8.70 g of 2-fluoro-4'-methylbiphenyl, 8.32 g of N-bromosuccinimide, 0.10 g of 2,2'-azobisisobutylonitrile and 150 ml of carbon tetrachloride was heat-refluxed for 5 hours. The reaction solution was washed with water, and the organic layer was concentrated. The resulting residue was purified through silica-gel column chromatography (eluent: a mixture of hexane and ethyl acetate at a ratio of 9:1) to obtain crude 2-fluoro-4'-bromomethylbiphenyl. Further, this compound was crystallized from hexane to give 4.93 g of 2-fluoro-4'-bromomethylbiphenyl.

Properties of the compound:

^{1}H-NMR($CDCl_3$, δ): 4.55(2H, s), 7.13–7.23(2H, m), 7.33 (1H, m), 7.43(1H, m), 7.47(2H, d, J=8.1 Hz), 7.54(2H, d, J=8.1 Hz).

PRODUCTION EXAMPLE 49

Production of ethyl 3-[N-[(2'-fluorobiphenyl-4-yl) methyl]acetylamino]-4-nitrobenzoate

Ethyl 3-[N-[2'-fluorobiphenyl-4-yl)methyl]acetylamino]-4-nitrobenzoate (1.90 g) was formed from 1.54 g of ethyl 3-acetylamino-4-nitrobenzoate and 2.26 g of 2-fluoro-4'-bromomethylbiphenyl in the same manner as in Production Example 14.

Properties of the compound:

^{1}H-NMR($CDCl_3$, δ): 1.33(3H, t, J=7.1 Hz), 1.92(3H, s), 4.36(2H, m), 4.44(1H, d, J=4.4 Hz), 5.32(1H, d, J=4.4 Hz), 7.13(1H, m), 7.18–7.22(3H, m), 7.31(1H, m), 7.40(1H, dt, J=1.6 and 7.7 Hz), 7.44(2H, d), 7.67(1H, d, J=1.6 Hz), 7.94(1H, d, J=8.4 Hz), 8.15(1H, dd, J=1.8 and 8.4 Hz).

EXAMPLE 244

Synthesis of 6-ethoxycarbonyl-1-[(2'-fluorobiphenyl-4-yl)methyl]-2-methylbenzimidazole (306)

In the same manner as in Example 24, 1.53 g of 6-ethoxycarbonyl-1-[(2'-fluorobiphenyl-4-yl)methyl]-2-methylbenzimidazole (306) were formed from 1.90 g of ethyl 3-[N-[2'-fluorobiphenyl-4-yl)methyl]acetylamino]-4-nitrobenzoate.

Properties of Compound (306):

^{1}H-NMR($CDCl_3$, δ): 1.40(3H, t, J=7.1 Hz), 2.62(3H, s), 4.38(2H, q, J=7.1 Hz), 5.43(2H, s), 7.10–7.17(3H, m), 7.19(1H, dt, J=1.0 and 7.5 Hz), 7.31(1H, m), 7.38(1H, dt, J=1.8 and 7.8 Hz), 7.50(2H, dd), 7.74(1H, d, J=8.5 Hz), 8.00(1H, dd, J=1.4 and 8.4 Hz), 8.06(1H, s).

EXAMPLE 245

Synthesis of 6-carboxy-1-[(2'-fluorobiphenyl-4-yl) methyl]-2-methylbenzimidazole (307)

In the same manner as in Example 53, 1.24 g of 6-carboxy- 1-[(2'-fluorobiphenyl-4-yl)methyl]-2-methylbenzimidazole (307) were formed from 1.50 g of 6-ethoxycarbonyl-1-[(2'-fluorobiphenyl-4-yl)methyl]-2-methylbenzimidazole.

Properties of Compound (307):

^{1}H-NMR(DMSO-d6, δ): 2.59(3H, s), 5.63(2H, s), 7.19 (2H, d, J=8.1 Hz), 7.24–7.31(2H, m), 7.39(1H, m), 7.46–7.53(3H, m), 7.62(1H, d, J=8.4 Hz), 7.80(1H, dd, J=1.3 and 8.4 Hz), 8.10(1H, s).

EXAMPLE 246

Synthesis of 6-(1-ethanesulfonylcarbamoyl)-1-[(2'-fluorobiphenyl-4-yl)methyl]-2-methylbenzimidazole (308)

In the same manner as in Example 98, 0.340 g of 6-(1-ethanesulfonylcarbamoyl)-1-[(2'-fluorobiphenyl-4-yl) methyl]-2-methylbenzimidazole (308) were formed from 0.455 g of 6-carboxy-1-[(2'-fluorobiphenyl-4-yl)methyl]-2-methylbenzimidazole, 0.409 g of N,N'-carbonyldiimidazole, 0.346 g of 1-butanesulfonamide and 0.384 g of diazabicycloundecene.

Properties of Compound (308):

^{1}H-NMR(DMSO-d6, δ): 0.84(3H, t, J=7.3 Hz), 1.39(1H, m), 1.67(1H, m), 2.57(3H, s), 3.51(1H, t), 5.60(2H, s), 7.21(2H, d, J=8.0 Hz), 7.24–7.30(2H, m), 7.39(1H, m), 7.48(1H, t), 7.52(2H, d, J=8.0 Hz), 7.66(1H, d, J=8.5 Hz), 7.80(1H, d, J=8.5 Hz), 8.25(1H, s), 11.93(1H, br s).

PRODUCTION EXAMPLE 50

Production of 3-fluoro-4-methylbiphenyl

Thirty milliliters of a 1.6-M-n-butyllithium hexane solution and a solution of 9.21 g of 4-bromo-2-fluorotoluene in 30 ml of tetrahydrofuran were added in this order to 30 ml of tetrahydrofuran which had been cooled to −78° C. in a nitrogen atmosphere, and the mixture was then stirred at −78° C. for 1 hour. A solution containing 6.64 g of zinc chloride which had been dehydrated through heat-melting under reduced pressure in 30 ml of tetrahydrofuran was added thereto at −78° C., and the mixture was stirred at room temperature for 1 hour. The reaction solution was added to a solution of 6.63 g of iodobenzene and 0.52 g of tetrakis (triphenylphosphine)palladium (0) in 30 ml of tetrahydrofuran at room temperature, and the mixed solution was stirred for 24 hours. The reaction solution was diluted with 300 ml of ethyl acetate, and the dilute solution was extracted with the addition of 10% hydrochloric acid. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried, and then concentrated. The residue was purified through silica-gel column chromatography (eluent: hexane) to give 6.00 g of oily 3-fluoro-4-methylbiphenyl.

Properties of the compound:

^{1}H-NMR($CDCl_3$, δ): 2.31(3H, d, J=1.8 Hz), 7.20–7.28 (3H, m), 7.34(1H, m), 7.43(2H, t), 7.55(2H, d)

PRODUCTION EXAMPLE 51

Production of 4-bromomethyl-3-fluorobiphenyl

A mixture of 6.00 g of 3-fluoro-4-methylbiphenyl, 5.73 g of N-bromosuccinimide, 0.075 g of 2,2'-azobisisobutylonitrile and 120 ml of carbon tetrachloride was heat-refluxed for 5 hours. The reaction solution was washed with water, and the organic layer was concentrated. The resulting residue was purified through silica-gel column chromatography (eluent: a mixture of hexane and ethyl acetate at a ratio of 9:1) to give 8.30 g of oily 4-bromomethyl-3-fluorobiphenyl.

Properties of the compound:

^{1}H-NMR($CDCl_3$, δ): 4.57(2H, s), 7.30(1H, d, J=11.0 Hz), 7.34–7.40(2H, m), 7.45(3H, m), 7.56(2H, d)

PRODUCTION EXAMPLE 52

Production of ethyl 3-[N-[(3-fluorobiphenyl-4-yl) methyl]acetylamino]-4-nitrobenzoate

In the same manner as in Production Example 14, 2.68 g of crude ethyl 3-[N-[3-fluorobiphenyl-4-yl)methyl] acetylamino]-4-nitrobenzoate were obtained from 1.54 g of ethyl 3-acetylamino-4-nitrobenzoate and 2.26 g of 3-fluoro-4-bromomethylbiphenyl.

EXAMPLE 247

Synthesis of 6-ethoxycarbonyl-1-[(3-fluorobiphenyl-4-yl)methyl]-2-methylbenzimidazole (309)

In the same manner as in Example 24, 1.34 g of 6-ethoxycarbonyl-1-[(3-fluorobiphenyl-4-yl)methyl]-2-methylbenzimidazole (309) were formed from 2.68 g of crude ethyl 3-[N-[3-fluorobiphenyl-4-yl)methyl] acetylamino]-4-nitrobenzoate.

Properties of Compound (309):

^{1}H-NMR($CDCl_3$, δ): 1.40(3H, t, J=7.1 Hz), 2.65(3H, s), 4.39(2H, q, J=7.1 Hz), 5.46(2H, s), 6.79(1H, t, J=8.0 Hz), 7.25(1H, m), 7.34–7.40(2H, m), 7.41–7.47(2H, m), 7.50–7.54(2H, m), 7.74(1H, d, J=8.5 Hz), 7.99(1H, dd, J=1.5 and 8.4 Hz), 8.07(1H, d, J=1.3 Hz).

EXAMPLE 248

Synthesis of 6-carboxy-1-[(3-fluorobiphenyl-4-yl) methyl]-2-methylbenzimidazole (310)

In the same manner as in Example 53, 1.15 g of 6-carboxy-1-[(3-fluorobiphenyl-4-yl)methyl]-2-methylbenzimidazole (310) were formed from 1.34 g of 6-ethoxycarbonyl-1-[(3-fluorobiphenyl-4-yl)methyl]-2-methylbenzimidazole.

Properties of Compound 310:

^{1}H-NMR(DMSO-d6, δ): 2.59(3H, s), 5.64(2H, s), .7.03 (1H, t, J=8.0 Hz), 7.37(1H, t, J=7.3 Hz), 7.42–7.48(3H, m), 7.56–7.68(4H, m), 7.79(1H, dd, J=1.4 and 8.4 Hz), 8.11(1H, s), 12.7(1H, br s).

EXAMPLE 249

Synthesis of 6-(1-butanesulfonylcarbamoyl)-1-[(3-fluorobiphenyl-4-yl)methyl]-2-methylbenzimidazole (311)

In the same manner as in Example 98, 0.236 g of 6-(1-butanesulfonylcarbamoyl)-1-[(3-fluorobiphenyl-4-yl)

methyl]-2-methylbenzimidazole (311) were formed from 0.390 g of 6-carboxy-1-[(3-fluorobiphenyl-4-yl)methyl]-2-methylbenzimidazole, 0.351 g of N,N'-carbonyldiimidazole, 0.297 g of 1-butanesulfonamide and 0.329 g of diazabicycloundecene.

Properties of Compound (311):

^{1}H-NMR(DMSO-d6, δ): 0.84(3H, t), 1.38(2H, m), 1.65 (2H, m), 2.57(3H, s), 3.48(2H, m), 5.63(2H, s), 6.93(1H, t, J=8.1 Hz), 7.37(1H, m), 7.42–7.47(3H, m), 7.60(1H, dd, J=1.7 and 11.8 Hz), 7.62–7.68(3H, m), 7.80(1H, dd, J=1.5 and 8.4 Hz), 8.21(1H, d, J=1.3 Hz), 11.90(1H, br s).

IR(Nujol): 1681 cm^{-1}.

mp: 227–230° C.

EXAMPLE 250

Synthesis of 1-(2-chlorobenzyl)-6-[(2-methoxyethane)sulfonylcarbamoyl]-2-methylbenzimidazole (312)

In the same manner as in Example 98, 0.149 g of 1-(2-chlorobenzyl)-6-[(2-methoxyethane)sulfonylcarbamoyl]-2-methylbenzimidazole (312) were formed from 0.300 g of 1-(biphenyl-4-ylmethyl)-6-carboxy-2-ethylbenzimidazole, 0.272 g of N,N'-carbonyldiimidazole, 0.258 g of (2-ethoxyethane)sulfonamide and 0.256 g of diazabicycloundecene.

Properties of Compound (312):

^{1}H-NMR(DMSO-d6, δ): 0.87(3H, t, J=6.9 Hz), 1.30(3H, t, J=8.0 Hz), 2.89(2H, q, J=7.6 Hz), 3.25–3.35(2H, m), 3.63–3.74(2H, m), 5.59(2H, s), 7.17(2H, d, J=8.1 Hz), 7.34(1H, t, J=7.0 Hz), 7.44(2H, t, J=7.6 Hz), 7.58–7.68(5H, m), 7.82(1H, d, J=8.4 Hz), 8.23(1H, s), 11.88(1H, s).

IR(Nujol): 1681 cm^{-1}.

mp: 78–81° C.

EXAMPLE 251

Synthesis of 1-(2,4-dichlorobenzyl)-2-methyl-6-(1-pentanesulfonylcarbamoyl)benzimidazole (313)

In the same manner as in Example 98, 0.196 g of 1-(2,4-dichlorobenzyl)-2-methyl-6-(1-pentanesulfonylcarbamoyl)benzimidazole (313) were formed from 0.300 g of 6-carboxy-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole, 0.323 g of N,N'-carbonyldiimidazole, 0.301 g of 1-pentanesulfonamide and 0.303 g of diazabicycloundecene.

Properties of Compound (313):

^{1}H-NMR(DMSO-d6, δ): 0.81(3H, t, J=7.3 Hz), 1.22–1.30 (2H, m), 1.32–1.39(2H, m), 1.64–1.71(2H, m), 2.50(3H, s), 3.50(2H, t, J=7.8 Hz), 5.59(2H, s), 6.45(1H, d, J=8.4 Hz), 7.33(1H, dd, J=2.2 and 8.5 Hz), 7.69(1H, d, J=8.5 Hz), 7.76(1H, d, J=2.1 Hz), 7.80(1H, dd, J=1.6 and 8.5 Hz), 8.10(1H, s), 11.89(1H, s).

IR(Nujol): 1682 cm^{-1}.

mp: 213.2–214.6° C.

EXAMPLE 252

Synthesis of 1-(biphenyl-4-ylmethyl)-2-ethyl-6-[1-[3-(methylthio)propane]sulfonylcarbamoyl]benzimidazole (314)

In the same manner as in Example 98, 0.178 g of 1-(biphenyl-4-ylmethyl)-2-ethyl-6-[1-[3-(methylthio)propane]sulfonylcarbamoyl]benzimidazole (314) were formed from 0.300 g of 6-carboxy-1-(biphenyl-4-ylmethyl)-2-ethylbenzimidazole, 0.272 g of N,N'-carbonyldiimidazole, 0.285 g of 1-[(3-methylthio)propane]sulfonamide and 0.256 g of diazabicycloundecene.

Properties of Compound (314):

^{1}H-NMR(DMSO-d6, δ): 1.30(3H, t, J=7.5 Hz), 1.91–1.99 (2H, m), 1.97(3H, s), 2.58(2H, t, J=7.2 Hz), 2.90(2H, q, J=7.6 Hz), 3.55–3.61(2H, m), 5.60(2H, s), 7.18(2H, d, J=8.2 Hz), 7.35(1H, t, J=7.3 Hz), 7.44(2H, t, J=7.5 Hz), 7.60–7.66 (4H, m), 7.69(1H, d, J=8.5 Hz), 7.82(1H, dd, J=1.8 and 8.5 Hz), 8.24(1H, s), 11.98(1H, s).

IR(Nujol): 1671 cm^{-1}.

mp: 89.9–91.2° C.

EXAMPLE 253

Synthesis of 1-(4-biphenylmethyl)-2-ethyl-6-(1-pentanesulfonylcarbamoyl)benzimidazole (315)

In the same manner as in Example 98, 0.258 g of 1-(4-biphenylmethyl)-2-ethyl-6-(1-pentanesulfonylcarbamoyl)benzimidazole (315) were formed from 0.300 g of 6-carboxy-1-(4-biphenylmethyl)-2-ethylbenzimidazole, 0.272 g of N,N'-carbonyldiimidazole, 0.254 g of 1-pentanesulfonamide and 0.256 g of diazabicycloundecene.

Properties of Compound (315):

^{1}H-NMR(DMSO-d6, δ): 0.87(3H, t, J=7.2 Hz), 1.22–1.39 (4H, m), 1.30(3H, t, J=7.5 Hz), 1.66–1.73(2H, m), 2.90(2H, q, J=7.4 Hz), 3.51(2H, t, J=7.7 Hz), 5.60(2H, s), 7.18(2H, d, J=8.2 Hz), 7.34(1H, t, J=7.4 Hz), 7.44(2H, t, J=7.6 Hz), 7.60–7.67(4H, m), 7.71(1H, d, J=8.4 Hz), 7.81(1H, dd, J=1.6 and 8.4 Hz), 8.27(1H, d, J=1.1 Hz), 11.92(1H, s).

IR(Nujol): 1682 cm^{-1}.

mp: 175.3–178.4° C.

EXAMPLE 254

Synthesis of 6-(1-butanesulfonylcarbamoyl)-1-(2,4-dicyclobenzyl)-2-ethylbenzimidazole (316)

In the same manner as in Example 98, 0.253 g of 6-(1-butanesulfonylcarbamoyl)-1-(2,4-dicyclobenzyl)-2-ethylbenzimidazole (316) were formed from 0.300 g of 6-carboxy-1-(2,4-dichlorobenzyl)-2-ethylbenzimidazole, 0.258 g of N,N'-carbonyldiimidazole, 0.217 g of 1-butanesulfonamide and 0.262 g of diazabicycloundecene.

Properties of Compound (316):

^{1}H-NMR(DMSO-d6, δ): 0.85(3H, t, J=7.4 Hz), 1.27(3H, t, J=7.4 Hz), 1.35–1.43(2H, m), 1.63–1.70(2H, m), 2.81(2H, q, J=7.4 Hz), 3.51(2H, t, J=7.7 Hz), 5.59(2H, s), 6.41(1H, d, J=8.4 Hz), 7.32(1H, dd, J=2.0 and 8.4 Hz), 7.73(1H, d, J=8.4 Hz), 7.76(1H, d, J=2.0 Hz), 7.81(1H, dd, J=1.5 and 8.5 Hz), 8.12(1H, d, J=1.6 Hz), 11.87(1H, s).

IR(Nujol) 1694 cm^{-1}.

mp: 175.7–176.9° C.

EXAMPLE 255

Synthesis of 1-(4-biphenylmethyl)-2-ethyl-6-[1-(3-methyl)butanesulfonylcarbamoyl]benzimidazole (317)

In the same manner as in Example 98, 0.273 g of 1-(4-biphenylmethyl)-2-ethyl-6-[1-(3-methyl)butanesulfonylcarbamoyl]benzimidazole (317) were formed from 0.300 g of 1-(4-biphenylmethyl)-6-carboxy-2-

ethylbenzimidazole, 0.272 g of N,N'-carbonyldiimidazole, 0.254 g of 1-(3-methyl)butanesulfonamide and 0.256 g of diazabicycloundecene.

Properties of Compound (317):

^{1}H-NMR(DMSO-d6, δ): 0.85(6H, d, J=6.5 Hz), 1.30(3H, t, J=7.4 Hz), 1.55–1.62(2H, m), 1.63–1.70(1H, m), 2.90(2H, q, J=7.4 Hz), 3.52(2H, t, J=7.9 Hz), 5.61(2H, s), 7.19(2H, d, J=8.3 Hz), 7.35(1H, t, J=7.4 Hz), 7.44(2H, t, J=7.5 Hz), 7.61–7.66(4H, m), 7.71(1H, d, J=8.5 Hz), 7.81(1H, dd, J=1.6 and 8.4 Hz), 8.27(1H, s), 11.95(1H,

IR(Nujol): 1682 cm^{-1}.

mp: 102.8–104.5° C.

EXAMPLE 256

Synthesis of 1-(2,4-dichlorobenzyl)-5-ethoxycarbonyl-2-methylbenzimidazole (318)

In the same manner as in Production Example 14, ethyl 4-[N-(2,4-dichlorobenzyl)acetylamino]-3-nitrobenzoate was formed from 1.525 g of ethyl 4-acetylamino-3-nitrobenzoate and 1.42 g of 2,4-dichlorobenzyl chloride. This compound was converted into 1-(2,4-dichlorobenzyl)-5-ethoxycarbonyl-2-methylbenzimidazole [(318), 1.476 g] in the same manner as in Example 24 without being purified.

Properties of Compound (318):

^{1}H-NMR($CDCl_3$, δ): 1.42(3H, t, J=7.1 Hz), 2.57(3H, s), 4.41(2H, q, J=7.1 Hz), 5.38(2H, s), 6.35(1H, d, J=8.4 Hz), 7.09(1H, dd, J=2.0 and 8.4 Hz), 7.16(1H, d, J=8.9 Hz), 7.49(1H, d, J=2.0 Hz), 7.96(1H, dd, J=1.5 and 8.5 Hz), 8.46(1H, s).

EXAMPLE 257

Synthesis of 5-carboxy-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole (319)

In the same manner as in Example 53, 1.195 g of 5-carboxy-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole (319) were formed from 1.465 g of 1-(2,4-dichlorobenzyl)-5-ethoxycarbonyl-2-methylbenzimidazole.

Properties of Compound (319):

^{1}H-NMR(DMSO-d6, δ): 2.48(3H, s), 5.56(2H, s), 6.53 (1H, d, J=8.4 Hz), 7.32(1H, dd, J=2.1 and 8.4 Hz), 7.44(1H, d, J=8.4 Hz), 7.73(1H, d, J=2.2 Hz), 7.78(1H, dd, J=1.5 and 8.4 Hz), 8.15(1H, d, J=1.3 Hz).

EXAMPLE 258

Synthesis of 5-(1-butanesulfonylcarbamoyl)-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole (320)

In the same manner as in Example 98, 0.690 g of 5-(1-butanesulfonylcarbamoyl)-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole (320) were formed from 0.565 g of 5-carboxy-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole, 0.504 g of N,N'-carbonyldiimidazole, 0.427 g of 1-butanesulfonamide and 0.473 g of diazabicycloundecene.

Properties of Compound (320):

^{1}H-NMR(DMSO-d6, δ): 0.87(3H, t, J=7.3 Hz), 1.41(2H, m), 1.68(2H, m), 2.49(3H, s), 3.52(2H, m), 5.58(2H, s), 6.53(1H, d, J=8.4 Hz), 7.33(1H, dd, J=2.1 and 8.4 Hz), 7.50(1H, d, J=8.5 Hz), 7.73(1H, d, J=2.1 Hz), 7.78(1H, dd, J=1.5 and 8.5 Hz), 8.24(1H, s), 11.97(1H, br s).

IR(Nujol): 1674 cm^{-1}.

mp: 135.4–139.2° C.

EXAMPLE 259

Synthesis of 1-(4-biphenylmethyl)-5-ethoxycarbonyl-2-ethylbenzimidazole (321)

In the same manner as in Production Example 14, ethyl 4-[N-(4-biphenylmethyl)propionylamino]-3-nitrobenzoate was formed from 1.50 g of 4-propionylamino-3-nitrobenzoate and 1.67 g of 4-bromomethylbiphenyl. This compound was converted into 1-(4-biphenylmethyl)-5-ethoxycarbonyl-2-ethylbenzimidazole [(321), 1.23 g] in the same manner as in Example 24 without being purified.

Properties of Compound (321):

^{1}H-NMR($CDCl_3$, δ): 1.40(3H, t, J=7.1 Hz), 1.45(3H, t, J=7.6 Hz), 2.90(2H, q, J=7.6 Hz), 4.39(2H, q, J=7.1 Hz), 5.40(2H, s), 7.09(2H, d, J=8.2 Hz), 7.27(1H, d, J=8.8 Hz), 7.34(1H, m), 7.42(2H, t), 7.55–7.51(4H, m), 7.97(1H, dd, J=1.5 and 8.4 Hz), 8.52(1H, d, J=1.2 Hz).

EXAMPLE 260

Synthesis of 1-(4-biphenylmethyl)-5-carboxy-2-ethylbenzimidazole (322)

In the same manner as in Example 53, 0.870 g of 1-(4-biphenylmethyl)-5-carboxy-2-ethylbenzimidazole (322) were formed from 1.00 g of 1-(4-biphenylmethyl)-5-ethoxycarbonyl-2-ethylbenzimidazole.

Properties of Compound (322):

^{1}H-NMR(DMSO-d6, δ): 1.30(3H, t, J=7.4 Hz), 2.90(2H, q, J=7.4 Hz), 5.57(2H, s), 7.17(2H, d, J=8.3 Hz), 7.33(1H, m), 7.42(2H, t), 7.63–7.57(5H, m), 7.81(1H, dd, J=1.6 and 8.6 Hz), 8.18(1H, d, J=1.3 Hz), 12.67(1H, br s).

EXAMPLE 261

Synthesis of 1-(4-biphenylmethyl)-5-(1-butanesulfonylcarbamoyl)-2-ethylbenzimidazole (323)

In the same manner as in Example 98, 0.305 g of 1-(4-biphenylmethyl)-5-(1-butanesulfonylcarbamoyl)-2-ethylbenzimidazole (323) were formed from 0.400 g of 1-(4-biphenylmethyl)-5-carboxy-2-ethylbenzimidazole, 0.364 g of N,N'-carbonyldiimidazole, 0.308 g of 1-butanesulfonamide and 0.342 g of diazabicycloundecene.

Properties of Compound (323):

^{1}H-NMR(DMSO-d6, δ): 0.86(3H, t, J=7.4 Hz), 1.30(3H, t, J=7.5 Hz), 1.41(2H, m), 1.68(2H, m), 2.91(2H, q, J=7.4 Hz), 3.52(2H, m), 5.59(2H, s), 7.16(2H, d, J=8.2 Hz), 7.34(1H, t, J=7.4 Hz), 7.43(2H, t), 7.59–7.65(5H, m), 7.80 (1H, dd, J=1.6 and 8.6 Hz), 8.24(1H, d, J=1.6 Hz), 11.97(1H, br s).

IR(Nujol): 1682 cm^{-1}.

mp: 142.9–144.4° C.

EXAMPLE 262

Synthesis of 1-(4-biphenylmethyl)-2-ethyl-6-(2-methoxyethanesulfonylcarbamoyl)benzimidazole (324)

In the same manner as in Example 98, 0.487 g of 1-(4-biphenylmethyl)-2-ethyl-6-(2-methoxyethanesulfonylcarbamoyl)benzimidazole (324) were formed from 0.513 g of benzimidazole, 0.464 g of N,N'-carbonyldiimidazole, 0.420 g of 2-methoxyethanesulfonamide and 0.438 g of diazabicycloundecene.

Properties of Compound (324):

^{1}H-NMR(DMSO-d6, δ): 1.30(3H, t, J=7.5 Hz), 2.90(2H, q, J=7.4 Hz), 3.13(3H, s), 3.70–3.77(4H, m), 5.60(2H, s). 7.18(2H, d, J=8.2 Hz), 7.35(1H, t, J=7.1 Hz), 7.44(2H, t, J=7.5 Hz), 7.60–7.67(4H, m), 7.70(1H, d, J=8.5 Hz), 7.80 (1H, dd, J=7.4 and 1.3 Hz), 8.25(1H, s), 11.97(1H, s).

IR(Nujol): 1684 cm^{-1}.

mp: 94.6–97.2° C.

EXAMPLE 263

Synthesis of 6-ethoxycarbonyl-2-ethyl-1-[4-(4-fluorobenzyloxy)benzyl]benzimidazole (325)

A mixture of 0.534 g of ethyl 4-propionylamino-3-aminobenzoate, 0.374 g of potassium carbonate, 0.800 g of 4-(4-fluorobenzyloxy)benzyl bromide, 5 ml of ethyl acetate and 3 ml of water was stirred at 75° C. for 16 hours. The organic layer was concentrated, and ethanol and 0.46 g of 36% hydrochloric acid were added to the residue. The mixture was stirred for 2 hours while being heat-refluxed. The reaction mixture was neutralized with potassium carbonate, and the solvent was then concentrated under reduced pressure. The residue was extracted with ethyl acetate and with water. The organic layer was concentrated under reduced pressure, and was purified through silica-gel column chromatography (eluent: a mixture of hexane and ethyl acetate at a ratio of 1:1) to give 0.228 g of 6-ethoxycarbonyl-2-ethyl-1-[4-(4-fluorobenzyloxy)benzyl] benzimidazole (325).

Properties of Compound (325):

^{1}H-NMR($CDCl_3$, δ): 1.40(3H, t, J=7.1 Hz), 1.42(3H, t, J=7.5 Hz), 2.86(2H, q, J=7.5 Hz), 4.38(2H, q, J=7.1 Hz), 4.97(2H, s), 5.32(2H, s), 6.88(2H, d, J=8.7 Hz), 6.98(2H, d, J=8.7 Hz), 7.05(2H, t, J=8.7 Hz), 7.37(2H, m), 7.76(2H, d, J=8.4 Hz), 7.98(1H, dd, J=1.5 and 8.5 Hz), 8.02(1H, s).

EXAMPLE 264

Synthesis of 6-carboxy-2-ethyl-1-[4-(4-fluorobenzyloxy)benzyl]benzimidazole (326)

In the same manner as in Example 53, 0.175 g of 6-carboxy-2-ethyl-1-[4-(4-fluorobenzyloxy)benzyl] benzimidazole (326) were formed from 0.225 g of 6-ethoxycarbonyl-2-ethyl-1-[4-(4-fluorobenzyloxy)benzyl] benzimidazole.

Properties of Compound (326):

^{1}H-NMR(DMSO-d6, δ): 1.28(3H, t, J=7.4 Hz), 2.89(2H, q, J=7.4 Hz), 5.01(2H, s), 5.47(2H, S), 6.95(2H, d), 7.03(2H, d), 7.18(2H, t), 7.45(2H, m), 7.62(1H, d, J=8.4 Hz), 7.77 (1H, d, J=8.4 Hz), 8.05(1H, s).

EXAMPLE 265

Synthesis of 6-(1-butanesulfonylcarbamoyl)-2-ethyl-1-[4-(4-fluorobenzyloxy)benzyl]benzimidazole ammonium salt (327)

In the same manner as in Example 98, oily 6-(1-butanesulfonylcarbamoyl)-2-ethyl-1-[4-(4-fluorobenzyloxy)benzyl]benzimidazole was obtained from 0.171 g of 6-carboxy-2-ethyl-1-[4-(4-fluorobenzyloxy) benzyl]benzimidazole, 0.137 g of N,N'-carbonyldiimidazole, 0.116 g of butanesulfonamide and 0.129 g of diazabicycloundecene. This compound was dissolved in ethyl acetate, and aqueous ammonia was added thereto. The solid material precipitated was separated through filtration, and was dried to give 0.140 g of 6-(1-butanesulfonylcarbamoyl)-2-ethyl-1-[4-(4-fluorobenzyloxy)benzyl]benzimidazole ammonium salt (327).

Properties of Compound (327):

^{1}H-NMR(DMSO-d6, δ): 0.83(3H, t), 1.25(3H, t), 1.35 (2H, m),1.61(2H, m), 2.84(2H, q), 3.27(2H, m), 5.01(2H, s), 5.42(2H, s), 6.95(2H, d, J=7.8 Hz), 7.02(2H, d, J=7.8 Hz), 7.17(2H, t), 7.44(2H, m), 7.57(1H, d, J=8.1 Hz), 7.82(1H, d, J=8.1 Hz), 8.12(1H, s).

IR(Nujol): 1614 cm^{-1}.

mp: 105–115° C.

EXAMPLE 266

Synthesis of 1-[4-(3,4-dichlorobenzyloxy)benzyl]-6-ethoxycarbonyl-2-ethylbenzimidazole (328)

In the same manner as in Example 263, 2.01 g of 1-[4-(3,4-dichlorobenzyloxy)benzyl]-6-ethoxycarbonyl-2-ethylbenzimidazole (328) were formed from 1.81 g of ethyl 4-propionylamino-3-aminobenzoate and 3.18 g of 4-(3,4-dichlorobenzyloxy)benzyl bromide.

Properties of Compound (328):

^{1}H-NMR($CDCl_3$, δ): 1.40(3H, t, J=7.1 Hz), 1.42(3H, t, J=7.5 Hz), 2.86(2H, q, J=7.5 Hz), 4.38(2H, q, J=7.1 Hz), 4.97(2H, s), 5.33(2H, s), 6.87(2H, m), 6.98(2H, m), 7.22 (1H, dd, J=2.0 and 8.3 Hz), 7.44(1H, d, J=8.3 Hz), 7.50(1H, d, J=2.0 Hz), 7.76(1H, d, J=8.6 Hz), 7.97(1H, dd, J=1.6 and 8.6 Hz), 8.02(1H, d, J=1.3 Hz).

EXAMPLE 267

Synthesis of 6-carboxy-1-[4-(3,4-dichlorobenzyloxy)benzyl]-2-ethylbenzimidazole (329)

In the same manner as in Example 53, 1.82 g of 6-carboxy-1-[4-(3,4-dichlorobenzyloxy)benzyl]-2-ethylbenzimidazole (329) were formed from 2.01 g of 6-ethoxycarbonyl-2-ethyl-1-[4-(4-fluorobenzyloxy)benzyl] benzimidazole.

Properties of Compound (329):

^{1}H-NMR(DMSO-d6, δ): 1.28(3H, t), 2.88(2H, q), 5.05 (2H, s), 5.47(2H, s), 6.96(2H, d), 7.04(2H, d), 7.39(1H, m), 7.68–7.59(3H, m), 7.78(1H, d, J=8.4 Hz), 8.06(1H, s).

EXAMPLE 268

Synthesis of 6-(1-butanesulfonylcarbamoyl)-1-[4-(3,4-dichlorobenzyloxy)benzyl]-2-ethylbenzimidazole ammonium salt (330)

Oily 6-(1-butanesulfonylcarbamoyl)-1-[4-(3,4-dichlorobenzyloxy)benzyl]-2-ethylbenzimidazole was obtained from 0.500 g of 6-carboxy-1-[4-(3,4-dichlorobenzyloxy)benzyl]-2-ethylbenzimidazole, 0.356 g of N,N'-carbonyldiimidazole, 0.301 g of butanesulfonamide and 0.334 g of diazabicycloundecene in the same manner as in Example 98. This compound was dissolved in ethyl acetate, and aqueous ammonia was added thereto. The solid material precipitated was separated through filtration, and was dried to give 0.51 g of 6-(1-butanesulfonylcarbamoyl)-1-[4-(3,4-dichlorobenzyloxy)benzyl]-2-ethylbenzimidazole ammonium salt (330).

Properties of Compound (330)

^{1}H-NMR(DMSO-d6, δ): 0.82(3H, t, J=7.3 Hz), 1.26(3H, t, J=7.4 Hz), 1.31(2H, m), 1.54(2H, m), 2.84(2H, q, J=7.4 Hz), 3.07(2H, m), 5.05(2H, s), 5.41(2H, s), 6.95(2H, d, J=8.7 Hz), 7.00(2H, d, J=8.7 Hz), 7.41(1H, d, J=8.2 Hz), 7.46(1H, d, J=8.4 Hz), 7.62(1H, d, J=8.2 Hz), 7.68(1H, s), 7.81(1H, d, J=8.4 Hz), 7.97(1H, s).

IR(Nujol): 1540 cm^{-1}.

mp: 99.5–101.5° C.

EXAMPLE 269

Synthesis of 1-(4-biphenylmethyl)-6-(n-butylcarbamoyl)-2-ethylbenzimidazole (331)

In the same manner as in Example 15, 0.295 g of 1-(4-biphenylmethyl)-6-(n-butylcarbamoyl)-2-ethylbenzimidazole (331) were formed from 0.400 g of 1-(4-biphenylmethyl)-6-chlorocarbonyl-2-ethylbenzimidazole hydrochloride, 0.233 g of n-butylamine and 0.215 g of triethylamine.

Properties of Compound (331):

^{1}H-NMR(DMSO-d6, δ): 0.95(3H, t, J=7.3 Hz), 1.37–1.48 (2H, m), 1.45(3H, t, J=7.4 Hz), 1.57–1.63(2H, m), 2.90(2H, q, J=7.5 Hz), 3.46(2H, q, J=7.1 Hz), 5.42(2H, s), 6.16(1H, br s), 7.10(2H, d, J=8.1 Hz), 7.34(1H, t, J=7.5 Hz), 7.42(2H, t, J=7.5 Hz), 7.48–7.57(5H, m), 7.87(1H, d, J=8.4 Hz), 7.91(1H, s).

IR(Nujol): 1621 cm^{-1}.

mp: 170.5–173.0° C.

EXAMPLE 270

Synthesis of 1-(4-biphenylmethyl)-2-ethyl-6-(thiazol-2-ylcarbamoyl)benzimidazole (332)

In the same manner as in Example 15, 0.179 g of 1-(4-biphenylmethyl)-2-ethyl-6-(thiazol-2-ylcarbamoyl) benzimidazole (332) were obtained from 0.400 g of 1-(4-biphenylmethyl)-6-chlorocarbonyl-2-ethylbenzimidazole hydrochloride, 0.318 g of 2-aminothiazole and 0.215 g of triethylamine.

Properties of Compound (332):

^{1}H-NMR(DMSO-d6, δ): 1.48(3H, t, J=7.5 Hz), 2.95(2H, q, J=7.5 Hz), 5.41(2H, s), 6.94(1H, d, J=3.6 Hz), 7.06(2H, d, J=8.1 Hz), 7.26(1H, d, J=3.6 Hz), 7.32(1H, t, J=7.4 Hz), 7.39(2H, t, J=7.3 Hz), 7.47–7.51(4H, m), 7.87(2H, s), 8.03 (1H, s), 11.15(1H, s).

IR(Nujol): 1652 cm^{-1}.

mp: 225.5–227.7° C.

EXAMPLE 271

Synthesis of 1-(4-biphenylmethyl)-2-ethyl-6-(2-pyridylcarbamoyl)benzimidazole (333)

In the same manner as in Example 98, 0.116 g of 1-(4-biphenylmethyl)-2-ethyl-6-(2-pyridylcarbamoyl) benzimidazole (333) were formed from 0.300 g of 1-(4-biphenylmethyl)-6-carboxy-2-ethylbenzimidazole, 0.272 g of N,N'-carbonyldiimidazole, 0.158 g of 2-aminopyridine and 0.256 g of diazabicycloundecene.

Properties of Compound (333):

^{1}H-NMR($CDCl_3$, δ): 1.47(3H, t, J=7.6 Hz), 2.93(2H, q, J=7.4 Hz), 5.45(2H, s), 7.06(1H, dd, J=7.4 and 4.9 Hz), 7.10(2H, d, J=8.1 Hz), 7.34(1H, t, J=7.4 Hz), 7.42(2H, t, J=7.6 Hz), 7.50–7.55(4H, m), 7.75(1H, t, J=7.9 Hz), 7.79 (1H, d, J=8.4 Hz), 7.86(1H, d, J=8.4 Hz), 7.98(1H, s), 8.30(1H, d, J=6.2 Hz), 8.38(1H, d, J=8.4 Hz), 8.62(1H,s).

IR(Nujol): 1661 cm^{-1}.

mp: 160.9–164.5° C.

EXAMPLE 272

Synthesis of 6-(n-butylcarbamoyl)-1-(2,4-dichlorobenzyl)-2-methyl-benzimidazole (334)

In the same manner as in Example 15, 0.156 g of 6-(n-butylcarbamoyl)-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole (334) were formed from 0.300 g of 6-chlorocarbonyl-1-(2,4-dichlorobenzyl)-2-ethylbenzimidazole hydrochloride, 0.181 g of triethylamine and 0.196 g of n-butylamine.

Properties of Compound (334):

^{1}H-NMR($CDCl_3$, δ): 0.96(3H, t, J=7.3 Hz), 1.37–1.43 (2H, m), 1.55–1.62(2H, m), 2.56(3H, s), 3.46(2H, q, J=7.0 Hz), 5.40(2H, s), 6.15(1H, br s), 6.32(1H, d, J=8.5 Hz), 7.07(1H, d, J=8.4 Hz), 7.48(1H, d, J=2.0 Hz), 7.55(1H, d, J=8.4 Hz), 7.74(1H, d, J=8.4 Hz), 7.79(1H,s).

IR(Nujol): 1636 cm^{-1}.

mp: 146.6–147.5° C.

PRODUCTION EXAMPLE 53

Production of ethyl 3-[sec-(2,4-dichlorophenetyl) amino]-4-nitrobenzoate

A solution of 0.877 g of 3-fluoro-4-nitrobenzoic acid and 2.25 g of sec-(2,4-dichlorophenetyl)amine in 5 ml of toluene was heat-refluxed for 15 hours. After the solvent was distilled off, the residue was purified through silica-gel column chromatography to obtain crude 3-[sec-(2,4-dichlorophenetyl)amino]-4-nitrobenzoic acid. To this compound were added 80 ml of ethanol and 3.0 g of 97% sulfuric acid, and the mixture was heat-refluxed for 4.5 hours. After ethanol was distilled off under reduced pressure, the residue was extracted with chloroform and with a saturated aqueous solution of sodium hydrogencarbonate. The organic layer was dried, and was then concentrated under reduced pressure. The residue was purified through silica-gel column chromatography (eluent: a mixture of hexane and ethyl acetate at a ratio of 2:1) to give 1.16 g of ethyl 3-[sec-(2,4-dichlorophenetyl)amino]-4-nitrobenzoate.

Properties of the compound:

^{1}H-NMR($CDCl_3$, δ): 1.35(3H, t, J=7.1 Hz), 1.64(3H, d, J=6.6 Hz), 4.30(2H, q, J=7.1 Hz), 5.16(1H, m), 7.18–7.31 (4H, m), 7.43(1H, d, J=2.0 Hz), 8.21(1H, d, J=8.8 Hz), 8.34(1H, d, J=5 Hz).

PRODUCTION EXAMPLE 54

Production of ethyl 4-amino-3-[sec-(2,4-dichlorophenetyl)amino]benzoate

A mixture of 1.14 g of ethyl 3-[sec-(2,4-dichlorophenetyl) amino]-4-nitrobenzoate, 1.60 g of reduced iron, 10 ml of ethanol and 5 ml of acetic acid was heat-refluxed for 3 hours. The solid material was separated through filtration, and the filtrate was concentrated. The residue was extracted with chloroform and with 10% hydrochloric acid. The organic layer was washed with a saturated aqueous solution of sodium hydrogencarbonate, and the solvent was distilled off under reduced pressure. The residue was purified through silica-gel column chromatography (eluent: a mixture of hexane and ethyl acetate at a ratio of 2:1) to give 0.920 g of ethyl 4-amino-3-[sec-(2,4-dichlorophenetyl)amino] benzoate.

Properties of the compound:

^{1}H-NMR($CDCl_3$, δ): 1.31(3H, t, J=7.1 Hz), 1.52(3H, d, J=6.7 Hz), 3.56(1H, br s), 3.79(2H, br s), 4.23(2H, q, J=7.1 Hz), 4.96(1H, q, J=6.7 Hz), 6.68(1H, d, J=8.0 Hz), 7.03(1H, d, J=1.7 Hz), 7.15(1H, dd, J=2.1 and 8.4 Hz), 7.35(1H, d, J=8.4 Hz), 7.39–7.43(2H, m).

EXAMPLE 273

Synthesis of 1-[sec-(2,4-dichlorophenetyl)]-6-ethoxycarbonyl-2-methylbenzimidazole (335)

Acetyl chloride (0.243 g) was added dropwise to a solution of 0.900 g of ethyl 4-amino-3-[sec-2,4-dichlophenetyl)

amino]benzoate in 2.0 ml of pyridine at room temperature. Further, the mixture was stirred at room temperature for 1 hour, and the reaction mixture was then extracted with the addition of ethyl acetate and excess 10% hydrochloric acid. The organic layer was washed with a saturated aqueous solution of sodium hydrogencarbonate, and the solvent was distilled off under reduced pressure to obtain crude ethyl 4-4-acetylamino-3-[sec-(2,4-dichlorophenetyl)amino] benzoate. This crude product was immediately dissolved in 20 ml of ethanol, and 0.4 ml of 36% hydrochloric acid were added to the solution. The mixture was heat-refluxed for 2 hours. The reaction solution was neutralized with sodium hydrogencarbonate, and the solvent was distilled off under reduced pressure. The residue was extracted with ethyl acetate and with water. The organic layer was concentrated, and the residue was purified through silica-gel column chromatography (eluent: a mixture of ethyl acetate and methanol at a ratio of 20:1) to give 0.700 g of 1-[sec-(2,4-dichlorophenetyl)]-6-ethoxycarbonyl-2-methylbenzimidazole (335).

Properties of Compound (335):

^{1}H-NMR($CDCl_3$, δ): 1.38(3H, t, J=7.2 Hz), 2.01(3H, d, J=7.2 Hz), 2.63(3H, s), 4.29–4.40(2H, m), 5.89(1H, q, J=7.2 Hz), 7.37(1H, dd, J=2.2 and 8.4 Hz), 7.40(1H, d, J=2.0 Hz), 7.52(1H, d, J=8.4 Hz), 7.67(1H, d, J=8.4 Hz), 7.86(1H, s), 7.91(1H, dd, J=1.4 and 8.4 Hz).

EXAMPLE 274

Synthesis of 6-carboxy-1-[sec-(2,4-dichlorophenetyl)]-2-methylbenzimidazole (336)

In the same manner as in Example 53, 0.447 g of 6-carboxy-1-[sec-(2,4-dichlorophenetyl)]-2-methylbenzimidazole (336) were formed from 0.690 g of 1-[sec-(2,4-dichlorophenetyl)]-6-ethoxycarbonyl-2-methylbenzimidazole.

Properties of Compound (336):

^{1}H-NMR(DMSO-d6, δ): 1.88(3H, d, J=6.8 Hz), 2.57(3H, s), 6.01(1H, q), 7.55(1H, d), 7.60–7.67(3H, m), 7.71(1H, d), 7.89(1H, d), 12.65(1H, br s).

EXAMPLE 275

Synthesis of 6-(1-butanesulfonylcarbamoyl)-1-[sec-(2,4-dichlorophenetyl)]-2-methylbenzimidazole (337)

In the same manner as in Example 98, 6-(1-butanesulfonylcarbamoyl)-1-[sec-(2,4-dichlorophenetyl)]-2-methylbenzimidazole (336) was formed from 0.433 g of 6-carboxy-1-(sec-(2,4-dichlorophenetyl)]-2-methylbenzimidazole, 0.412 g of N,N'-carbonyldiimidazole, 0.348 g of butanesulfonamide and 0.386 g of diazabicycloundecene.

Properties of Compound (337)

^{1}H-NMR(DMSO-d6, δ): 0.84(3H, t, J=7.3 Hz), 1.34(2H, m), 1.57(2H, m), 1.89(3H, d, J=7.0 Hz), 2.49(3H, s), 3.07 (2H, m), 5.954(1H, q, J=7.0 Hz), 7.41(1H, d, J=8.7 Hz), 7.56(1H, dd, J=2.1 and 8.5 Hz), 7.61(1H, d, J=2.1 Hz), 7.74–7.79(3H, m).

EXAMPLE 276

Synthesis of 1-(4-biphenylmethyl)-2-ethyl-6-(phenylcarbamoyl)benzimidazole (338)

In the same manner as in Example 15, 0.195 g of 1-(4-biphenylmethyl)-2-ethyl-6-(phenylcarbamoyl) benzimidazole (338) were formed from 0.300 g of 1-(4-biphenylmethyl)-6-chlorocarbonyl-2-ethylbenzimidazole hydrochloride, 0.243 g of triethylamine and 0.224 g of aniline.

Properties of Compound (338):

^{1}H-NMR($CDCl_3$, δ): 1.47(3H, t, J=7.5 Hz), 2.93(2H, q, J=7.5 Hz), 5.44(2H, s), 7.11(2H, d, J=8.2 Hz), 7.14(1H, t, J=7.4 Hz), 7.32–7.38(3H, m), 7.42(2H, t, J=7.4 Hz), 7.51–7.54(4H, m), 7.63(2H, d, J=7.8 Hz), 7.69(1H, dd, J=8.4 and 1.6 Hz), 7.84(1H, d, J=8.4 Hz), 7.88(1H, br s), 7.97 (1H,d,J=1.5 Hz).

IR(Nujol): 1647 cm^{-1}.

mp: 171.7–172.1° C.

EXAMPLE 277

Synthesis of 1-(4-biphenylmethyl)-2-ethyl-6-(1,3,4-thiadiazol-2-ylcarbamoyl)benzimidazole (339)

In the same manner as in Example 98, 0.234 g of 1-(4-biphenylmethyl)-2-ethyl-6-(1,3,4-thiadiazol-2-ylcarbamoyl)benzimidazole (339) were formed from 0.300 g of 1-(4-biphenylmethyl)-6-carboxy-2-ethylbenzimidazole, 0.272 g of N,N'-carbonyldiimidazole, 0.170 g of 2-amino-1,3,4-thiadiazole and 0.256 g of diazabicycloundecene.

Properties of Compound (339):

^{1}H-NMR($CDCl_3$,δ): 1.45(3H, t, J=7.5 Hz), 2.90(2H, q, J=7.5 Hz), 5.53(2H,s), 7.07(2H, d, J=8.3 Hz), 7.33(1H, t, J=7.5 Hz), 7.40(2H, t, J=7.3 Hz), 7.52(4H, d, J=8.2 Hz), 7.89(1H, d, J=8.5 Hz), 8.08(1H, dd, J=8.5 and 1.6 Hz), 8.34(1H, d, J=1.2 Hz), 7.60(1H, s), 12.26(1H, s).

IR(Nujol): 1654 cm^{-1}.

mp: 230.1–233.4° C.

EXAMPLE 278

Synthesis of 1-(4-biphenylmethyl)-2-ethyl-6-(tetrazol-5-ylcarbamoyl)benzimidazole (340)

In the same manner as in Example 98, 0.135 g of 1-(4-biphenylmethyl)-2-ethyl-6-(tetrazol-5-ylcarbamoyl) benzimidazole (340) were formed from 0.300 g of 1-(4-biphenylmethyl)-6-carboxy-2-ethylbenzimidazole, 0.272 g of N,N'-carbonyldiimidazole, 0.143 g of 5-aminotetrazole and 0.256 g of diazabicycloundecene.

Properties of Compound (340)

^{1}H-NMR(DMSO-d6,δ): 1.32(3H, t, J=7.5 Hz), 2.93(2H, q, J=7.5 Hz), 5.61(2H, s), 7.23(2H, d, J=8.1 Hz), 7.34(1H, t, J=7.4 Hz), 7.44(2H, t, J=7.6 Hz), 7.60–7.67(4H, m), 7.76(1H, d, J=8.5 Hz), 7.98(1H, d, J=8.6 Hz), 8.46(1H, s), 12.30(1H, s), 15.95(1H, s).

IR(Nujol): 1667 cm^{-1}.

mp: 273.1–276.0° C.

EXAMPLE 279

Synthesis of 1-(4-biphenylmethyl)-2-ethyl-6-(1,3,4-triazol-3-ylcarbamoyl)benzimidazole (341)

In the same manner as in Example 98, 0.224 g of 1-(4-biphenylmethyl)-2-ethyl-6-(1,3,4-triazol-3-ylcarbamoyl)benzimidazole (341) were formed from 0.300 g of 1-(4-biphenylmethyl)-6-carboxy-2-ethylbenzimidazole, 0.272 g of N,N'-carbonyldiimidazole, 0.141 g of 3-amino-1,3,4-triazole and 0.256 g of diazabicycloundecene.

Properties of Compound (341):

^{1}H-NMR(DMSO-d6,δ): 1.33(3H, t, J=7.4Hz), 2.93(2H, q, J=7.4 Hz), 5.63(2H, s), 7.17(2H, d, J=8.3 Hz), 7.35(1H, t,

J=7.4 Hz), 7.44(2H, t, J=7.5 Hz), 7.60–7.65(4H, m), 7.78 (1H, d, J=7.4 Hz), 7.83(1H, dd, J=8.4 and 1.5 Hz), 8.17(1H, s), 8.77(2H, s), 12.04(1H, s).

IR(Nujol): 1675 cm^{-1}.

mp: 263.4–266.2° C.

EXAMPLE 280

Synthesis of 1-(4-biphenylmethyl)-2-ethyl-6-(1,3,4-triazol-2-ylcarbamoyl)benzimidazole (342)

In the same manner as in Example 98, 0.215 g of 1-(4-biphenylmethyl)-2-ethyl-6-(1,3,4-triazol-2-ylcarbamoyl)benzimidazole (342) were formed from 0.300 g of 1-(4-biphenylmethyl)-6-carboxy-2-ethylbenzimidazole, 0.272 g of N,N'-carbonyldiimidazole, 0.141 g of 2-amino-1,3,4-triazole and 0.256 g of diazabicycloundecene.

Properties of Compound (342):

^{1}H-NMR(DMSO-d6, δ): 1.31(3H, t, J=7.4 Hz), 2.92(2H, q, J=7.4 Hz), 5.60(2H, s), 7.23(2H, d, J=7.8 Hz), 7.34(1H, t, J=7.2 Hz), 7.44(2H, t, J=7.6 Hz), 7.60–7.66(4H, m), 7.72(1H, d, J=8.3 Hz), 7.78(1H, s), 7.95(1H, d, J=8.3 Hz), 8.43(1H, s), 11.85(1H, s), 13.57(1H, s).

IR(Nujol): 1659 cm^{-1}.

mp: 306.0° C.(decomp.).

EXAMPLE 281

Synthesis of 1-(4-biphenylmethyl)-2-ethyl-6-(3-pyridylcarbamoyl)benzimidazole (343)

In the same manner as in Example 98, 0.229 g of 1-(4-biphenylmethyl)-2-ethyl-6-(3-pyridylcarbamoyl) benzimidazole (343) were formed from 0.300 g of 1-(4-biphenylmethyl)-6-carboxy-2-ethylbenzimidazole, 0.272 g of N,N'-carbonyldiimidazole, 0.158 g of 3-aminopyridine and 0.256 g of diazabicycloundecene.

Properties of Compound (343):

^{1}H-NMR($CDCl_3$, δ): 1.47(3H, t, J=7.6 Hz), 2.93(2H, q, J=7.4 Hz), 5.45(2H, s), 7.10(2H, d, J=8.1 Hz), 7.29–7.36 (2H, m), 7.42(2H, t, J=7.4 Hz), 7.53(4H, d, J=8.0 Hz), 7.71(1H, d, J=8.5 Hz), 7.86(1H, d, J=8.4 Hz), 7.97(1H, s), 7.98(1H, s), 8.27(1H, d, J=8.4 Hz), 8.38(1H, d, J=4.7 Hz), 8.68(1H, d, J=2.5 Hz).

IR(Nujol): 1644 cm^{-1}.

mp: 124.4–125.6° C.

EXAMPLE 282

Synthesis of 1-(2,4-dichlorobenzyl)-2-methyl-6-(2-pyridylcarbamoyl)benzimidazole (344)

In the same manner as in Example 98, 0.152 g of 1-(2,4-dichlorobenzyl)-2-methyl-6-(2-pyridylcarbamoyl) benzimidazole (344) were formed from 0.300 g of 6-carboxy-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole, 0.290 g of N,N'-carbonyldiimidazole, 0.168 g of 2-aminopyridine and 0.273 g of diazabicycloundecene.

Properties of Compound (344):

^{1}H-NMR($CDCl_3$, δ): 2.59(3H, s), 5.43(2H, s), 6.33(1H, d, J=8.4 Hz), 7.06–7.10(2H, m), 7.50(1H, d, J=2.1 Hz), 7.77 (1H, dt, J=7.8 and 1.9 Hz), 7.83(2H, s), 7.88(1H, s), 8.30 (1H, d, J=3.7 Hz), 8.39(1H, d, J=8.3 Hz), 8.78(1H, s).

IR(Nujol): 1666 cm^{-1}.

mp: 157.4–159.2° C.

EXAMPLE 283

Synthesis of 1-(4-biphenylmethyl)-2-ethyl-6-(4-pyridylcarbamoyl)benzimidazole (345)

In the same manner as in Example 98, 0.153 g of 1-(4-biphenylmethyl)-2-ethyl-6-(4-pyridylcarbamoyl) benzimidazole (345) were formed from 0.300 g of 1-(4-biphenylmethyl)-6-carboxy-2-ethylbenzimidazole, 0.272 g of N,N'-carbonyldiimidazole, 0.158 g of 4-aminopyridine and 0.256 g of diazabicycloundecene.

Properties of Compound (345):

^{1}H-NMR($CDCl_3$, δ): 1.48(3H, t, J=7.4 Hz), 2.94(2H, q, J=7.4 Hz), 5.45(2H, s), 7.10(2H, d, J=8.1 Hz), 7.35(1H, t, J=7.4 Hz), 7.42(2H, t, J=7.4 Hz), 7.50–7.60(6H, m), 7.691 (1H, d, J=7.8 Hz), 7.86(1H, d, J=8.3 Hz), 7.95(1H, s), 7.99(1H, br s), 8.54(2H, dd, J=1.5 and 4.7 Hz).

IR(Nujol): 1663 cm^{-1}.

mp: 123.8–124.7° C.

PRODUCTION EXAMPLE 55

Production of N-(1-butanesulfonyl)-4-acetylamino-3-nitrobenzamide

In the same manner as in Production Example 28, 10.75 g of N-(1-butanesulfonyl)-4-acetylamino-3-nitrobenzamide were formed from 10.0 g of 4-acetylamino-3-nitrobenzoic acid, 9.40 g of N,N'-carbonyldiimidazole, 7.92 g of 1-butanesulfonamide and 8.83 g of diazabicycloundecene.

Properties of the compound:

^{1}H-NMR(DMSO-d6, δ): 0.87(3H, t, J=7.4 Hz), 1.37–1.44 (2H, m), 1.64–1.71(2H, m), 2.12(3H, s), 3.52(2H, t, J=7.7 Hz), 7.83(1H, d, J=8.6 Hz), 8.21(1H, dd, J=8.6 and 2.1 Hz), 8.54(1H, d, J=2.2 Hz), 10.56(1H, s), 12.32(1H, s).

PRODUCTION EXAMPLE 56

Production of N-(1-butanesulfonyl)-3-amino-4-acetylaminobenzamide

In the same manner as in Production Example 29, 3.04 g of N-(1-butanesulfonyl)-3-amino-4-acetylaminobenzamide were formed from 10.75 g of N-(1-butanesulfonyl)-4-acetylamino-3-nitrobenzamide.

Properties of the compound:

^{1}H-NMR(DMSO-d6, δ): 0.86(3H, t, J=7.3 Hz), 1.33–1.43 (2H, m), 1.59–1.67(2H, m), 2.07(3H, s), 3.37–3.43(2H, t), 5.12(2H, br s), 7.13(1H, dd, J=8.2 and 2.0 Hz), 7.28(1H, d, J=1.9 Hz), 7.40(1H, d, J=8.3 Hz), 9.09(1H, s).

PRODUCTION EXAMPLE 57

Production of N-(1-butanesulfonyl)-4-acetylamino-3-[4-(2-pyridyl)benzylamino]benzamide

In the same manner as in Production Example 32, crude N-(1-butanesulfonyl)-4-acetylamino-3-[4-(2-pyridyl) benzylamino]benzamide was obtained from 0.400 g of N-(1-butanesulfonyl)-3-amino-4-acetylaminobenzamide and 0.477 g of 2-[(4-bromomethyl)phenyl]pyridine. This product was used in the subsequent reaction at once.

EXAMPLE 284

Synthesis of 6-(1-butanesulfonylcarbamoyl)-1-[4-(2-pyridyl)benzyl]-2-methylbenzimidazole (346)

In the same manner as in Example 183, 0.330 g of 6-(1-butanesulfonylcarbamoyl)-1-[4-(2-pyridyl)benzyl]-2-methylbenzimidazole (346) were obtained from the above-mentioned crude N-(1-butanesulfonyl)-4-acetylamino-3-[4-(2-pyridyl)benzylamino]benzamide.

Properties of Compound (346):

^{1}H-NMR(DMSO-d6, δ): 0.82(3H, t), 1.37–1.46(2H, m), 1.54–1.61(2H, m), 2.54(3H, s), 3.10(2H, t, J=7.8 Hz), 5.57

(2H, s), 7.19(2H, d, J=7.5 Hz), 7.33(1H, t, J=5.2 Hz), 7.49(1H, d, J=8.4 Hz), 7.82–7.87(2H, m), 7.90(1H, d, J=8.0 Hz), 8.01–8.04(3H, m), 8.63(1H, d, J=4.2 Hz).

IR(Nujol): 1722 cm^{-1}.

mp: 292.4–298.4° C.

EXAMPLE 285

Synthesis of 5-chlorosulfonyl-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole (347) and 6-chlorosulfonyl-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole (348)

Four grams of 1-(2,4-dichlorobenzyl)-2-methylbenzimidazole were added to 20 ml of chlorosulfonic acid in an ice bath, and the mixture was stirred at room temperature for 24 hours and then at 80° C. for 1.5 hours. The reaction solution was poured into ice water, and the gum solid material precipitated was separated through filtration to obtain a mixture of 5-chlorosulfonyl-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole (347) and 6-chlorosulfonyl-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole (348). This mixture was used in the subsequent reaction at once.

EXAMPLE 286

Synthesis of 5-aminosulfonyl-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole (349) and 6-aminosulfonyl-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole (350)

The mixture of 5-chlorosulfonyl-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole and 6-chlorosulfonyl-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole obtained in Example 285 was immediately treated with 100 ml of 25% aqueous ammonia at room temperature for 1 hour. The solid material was separated through filtration to give 2.68 g of a mixture of 5-aminosulfonyl-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole (349) and 6-aminosulfonyl-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole (350) at a ratio of 1:1.

Properties of the mixture of Compound (349) and Compound (350):

^{1}H-NMR(CD3OD, δ): 2.52(3/2H, s), 2.54(3/2H, s), 5.54 (2H, s), 6.55(1H, d, J=6.9 Hz), 7.17(1H, d, J=8.0 Hz), 7.52(1H, s), 7.65–7.78(2H, m), 7.82(1/2H, s), 8.11(1/2H, s).

EXAMPLE 287

Synthesis of 6-(n-valerylaminosulfonyl)-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole (351) and 5-(n-valerylaminosulfonyl)-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole (352)

One milliliter of chloroform, 0.56 ml of triethylamine and 0.326 g of n-valeryl chloride were added to 0.500 g of a mixture of 5-aminosulfonyl-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole and 6-aminosulfonyl-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole at a ratio of 1:1, and the mixture was stirred at room temperature for 48 hours. Water was added thereto to stop the reaction, and the reaction solution was extracted with chloroform. The organic layer was dried, concentrated, and purified through silica-gel column chromatography (eluent: a mixture of chloroform and methanol at a ratio of 95:5) to obtain 0.360 g of a mixture of 5-(n-valerylaminosulfonyl)-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole and 6-(n-valerylaminosulfonyl)-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole. Further, this mixture was purified through medium-pressure silica-gel column chromatography (eluent: a mixture of hexane and ethyl acetate at a ratio of from 1:1 to 1:4) to give 0.95 g of 6-(n-valerylaminosulfonyl)-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole (351) and 0.45 g of 5-(n-valerylaminosulfonyl)-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole (352).

Properties of Compound (351):

^{1}H-NMR(DMSO-d6, δ): 0.74(3H, t, J=7.3 Hz), 1.09(2H, m), 1.31(2H, m), 2.10(2H, t, J=7.3 Hz), 2.53(3H, s), 5.63 (2H, s), 6.60(1H, d, J=8.4 Hz), 7.32(1H, d, J=8.3 Hz), 7.67–7.77(3H, m), 7.93(1H, s).

IR(KBr): 1726 cm^{-1}.

mp: 207.5–210.0° C.

Mass(FD): m/e 454(M+1).

Properties of Compound (352):

^{1}H-NMR(DMSO-d6, δ): 0.75(3H, t, J=7.3 Hz), 1.11(2H, m), 1.34(2H, m), 2.13(2H, t, J=7.4 Hz), 2.51(3H, s), 5.59 (2H, s), 6.57(1H, d, J=8.5 Hz), 7.32(1H, dd, J=2.2 and 8.4 Hz), 7.57(1H, d, J=8.6 Hz), 7.67(1H, dd, J=1.6 and 8.6 Hz), 7.73(1H, d, J=2.1 Hz), 8.08(1H, d, J=1.6 Hz).

IR(KBr): 1706 cm^{-1}.

mp: 213.0–216.0° C.

EXAMPLE 288

Synthesis of 2,4-dimethyl-6-methoxycarbonylbenzimidazole

Methyl 4-acetylamino-5-amino-3-methylbenzoate was obtained from methyl 4-amino-3-methylbenzoate by the method described in Journal of Medicinal Chemistry, 1993, 36, 4040–4051. Subsequently, this compound was heat-refluxed in acetic acid for 2 hours to give 2,4-dimethyl-6-methoxycarbonylbenzimidazole.

Properties of the compound:

^{1}H-NMR($CDCl_3$, δ): 2.55(3H, s), 2.62(3H, s), 3.91(3H, s), 7.74(1H, s), 8.07(1H, s), 10.65(1H, br s).

EXAMPLE 289

Synthesis of 1-(2,4-dichlorobenzyl)-2,4-dimethyl-6-methoxycarbonylbenzimidazole (353)

A mixture containing 0.900 g of 2,4-dimethyl-6-methoxycarbonylbenzimidazole, 1.20 g of 2,4-dichlorobenzyl chloride, 0.200 g of sodium iodide, 0.610 g of potassium carbonate and 4 ml of N,N-dimethylformamide was stirred at 80° C. for 16 hours. After the organic solvent was distilled off under reduced pressure, the residue was extracted with ethyl acetate and with water. The organic layer was concentrated, and was crystallized with the addition of hexane. The crystals were separated through filtration, and were dried to give 1.08 g of 1-(2,4-dichlorobenzyl)-2,4-dimethyl-6-methoxycarbonylbenzimidazole (353).

Properties of Compound (353):

^{1}H-NMR($CDCl_3$, δ): 2.58(3H, s), 2.71(3H, s), 3.90(3H, s), 5.39(2H, s), 6.30(1H, d, J=8.4 Hz), 7.07(1H, dd, J=8.4 and 2.0 Hz), 7.49(1H, d, J=2.0 Hz), 7.75(1H, s), 7.81(1H,s).

EXAMPLE 290

Synthesis of 6-carboxy-1-(2,4-dichlorobenzyl)-2,4-dimethylbenzimidazole (354)

In the same manner as in Example 53, 0.435 g of 6-carboxy-1-(2,4-dichlorobenzyl)-2,4-

dimethylbenzimidazole (354) were formed from 0.510 g of 1-(2,4-dichlorobenzyl)-2,4-dimethyl-6-methoxycarbonylbenzimidazole.

Properties of Compound (354):

^{1}H-NMR(DMSO-d6, δ): 2.51(3H, s), 2.55(3H, s), 5.57 (2H, s), 6.49(1H, d, J=8.4 Hz), 7.31(1H, dd, J=8.4 and 2.2 Hz), 7.62(1H, s), 7.72(1H, d, J=2.0 Hz), 7.78(1H, s), 12.64 (1H, br s).

EXAMPLE 291

Synthesis of 6-(1-butanesulfonylcarbamoyl)-1-(2,4-dichlorobenzyl)-2,4-dimethylbenzimidazole (355)

In the same manner as in Example 98, 0.468 g of 6-(1-butanesulfonylcarbamoyl)-1-(2,4-dichlorobenzyl)-2,4-dimethylbenzimidazole (355) were formed from 0.417 g of 6-carboxy-1-(2,4-dichlorobenzyl)-2,4-dimethylbenzimidazole, 0.290 g of N,N'-carbonyldiimidazole, 0.246 g of 1-butenesulfonamide and 0.273 g of diazabicycloundecene.

Properties of Compound (355):

^{1}H-NMR(DMSO-d6, δ): 0.84(3H, t, J=7.4 Hz), 1.38(2H, m), 1.64(2H, m), 2.49(3H, s), 2.56(3H, s), 3.48(2H, t), 5.55(2H, s), 6.40(1H, d, J=8.5 Hz), 7.31(1H, dd, J=2.1 and 8.4 Hz), 7.64(1H, s), 7.75(1H, d, J=2.1 Hz), 7.90(1H, s), 11.79(1H, br s).

IR(Nujol): 1682 cm^{-1}.

mp: 180.0–181.5° C.

PRODUCTION EXAMPLE 58

Production of 4-phenoxybenzyl alcohol

Sodium borohydride (0.48 g) was added to a solution of 4.96 g of 4-phenoxybenzaldehyde in 20 ml of ethanol, and the mixture was stirred at room temperature for 1.5 hours. After the completion of the concentration, the residue was extracted with tert-butylmethyl ether and with water. The organic layer was concentrated to give 4.84 g of 4-phenoxybenzyl alcohol.

Properties of the compound:

^{1}H-NMR($CDCl_3$, δ): 4.67(2H, d, J=5.7 Hz), 6.99–7.01 (4H, m), 7.10(1H, t, J=7.4 Hz), 7.32–7.35(4H, m).

PRODUCTION EXAMPLE 59

Production of 4-phenoxybenzyl chloride

Thionyl chloride (13.34 g) was added to 4.06 g of 4-phenoxybenzyl alcohol, and the mixture was stirred at 80° C. for 3.5 hours. After the completion of the concentration, the reaction mixture was extracted with ethyl acetate and with water. The organic layer was concentrated to give 4.31 g of 4-phenoxybenzyl chloride.

Properties of the compound:

^{1}H-NMR($CDCl_3$, δ): 4.58(2H, s), 6.96–7.03(4H, m), 7.11–7.14(1H, m), 7.32–7.37(4H, m).

EXAMPLE 292

Synthesis of 6-ethoxycarbonyl-2-methyl-1-(4-phenoxybenzyl)benzimidazole (356)

In the same manner as in Example 263, 0.49 g of ethyl 4-acetylamino-3-[(4-phenoxy)benzylamino]benzoate were obtained from 0.56 g of ethyl 4-acetylamino-3-aminobenzoate, 0.33 g of sodium carbonate, 0.12 g of sodium iodide and 0.66 g of 4-phenoxybenzyl chloride. Subsequently, this compound was converted into 6-ethoxycarbonyl-2-methyl-1-(4-phenoxybenzyl) benzimidazole [(356), 0.44 g].

Properties of ethyl 4-acetylamino-3-[(4-phenoxy) benzylamino]benzoate:

^{1}H-NMR($CDCl_3$, δ): 1.37(3H, t, J=7.1 Hz), 2.04(3H, s), 4.18(1H, br s), 4.31–4.36(4H, m), 6.98–7.02(4H, m), 7.09–7.12(1H, m), 7.27–7.51(8H, m).

Properties of Compound (356):

^{1}H-NMR($CDCl_3$, δ): 1.40(3H, t, J=7.1 Hz), 2.61(3H, s), 4.39(2H, q, J=7.1 Hz), 5.35(2H, s), 6.92–6.95(2H, m), 6.97–7.00(2H, m), 7.02(2H, d, J=8.7 Hz), 7.09–7.13(1H, m), 7.31–7.34(2H, m), 7.72(1H, d, J=8.6 Hz), 7.98(1H, dd, J=1.5 and 8.4 Hz), 8.04(1H, d, J=1.2 Hz).

EXAMPLE 293

Synthesis of 6-carboxy-2-methyl-1-(4-phenoxybenzyl)benzimidazole (357)

In the same manner as in Example 53, 0.37 g of 6-carboxy-2-methyl-1-(4-phenoxybenzyl)benzimidazole (357) were formed from 0.44 g of 6-ethoxycarbonyl-2-methyl-1-(4-phenoxy)benzylbenzimidazole.

Properties of Compound (357):

^{1}H-NMR(DMSO-d6, δ): 2.57(3H, s), 5.54(2H, s), 6.95–6.97(4H, m), 7.09–7.13(3H, m), 7.33–7.37(2H, m), 7.60(1H, d, J=8.4 Hz), 7.78(1H, d, J=8.4 Hz), 8.07(1H, s), 12.72(1H, br s).

EXAMPLE 294

Synthesis of 6-(1-butanesulfonylcarbamoyl)-2-methyl-1-(4-phenoxybenzyl)benzimidazole (358)

In the same manner as in Example 98, 0.19 g of 6-(1-butanesulfonylcarbamoyl)-2-methyl-1-(4-phenoxybenzyl) benzimidazole (358) were obtained from 0.36 g of 6-carboxy-2-methyl-1-(4-phenoxybenzyl)benzimidazole, 0.24 g of N,N'-carbonyldiimidazole, 0.21 g of 1-butanesulfonamide and 0.23 g of diazabicycloundecene.

Properties of Compound (358):

^{1}H-NMR(DMSO-d6, δ): 0.85(3H, t, J=7.4 Hz), 1.40(2H, m), 1.68(2H, m), 2.54(3H, s), 3.52(2H, t, J=7.8 Hz), 5.51 (2H, s), 6.96–6.98(4H, m), 7.11(1H, t, J=7.4 Hz), 7.17(2H, d, J=8.6 Hz), 7.34–7.37(2H, m), 7.64(1H, d, J=8.5 Hz), 7.79(1H, dd, J=1.5 and 8.5 Hz), 8.24(1H, s), 11.92(1H, br s).

IR(Nujol): 1632 cm^{-1}.

mp: 183.4–184.4° C.

EXAMPLE 295

Synthesis of 6-ethoxycarbonyl-2-methyl-1-(2-pyridylmethyl)benzimidazole (359)

In the same manner as in Example 263, 0.656 g of 6-ethoxycarbonyl-2-methyl-1-(2-pyridylmethyl) benzimidazole (359) were formed from 0.600 g of ethyl 4-acetylamino-3-aminobenzoate, 0.450 g of potassium carbonate, 0.122 g of sodium iodide and 0.413 g of 2-chloromethylpyridine. This compound was used in the subsequent reaction at once.

EXAMPLE 296

Synthesis of 6-carboxy-2-methyl-1-(2-pyridylmethyl)benzimidazole (360)

In the same manner as in Example 53, 0.532 g of 6-carboxy-2-methyl-1-(2-pyridylmethyl)benzimidazole

(360) were formed from 0.656 g of 6-ethoxycarbonyl-2-methyl-1-(2-pyridylmethyl)benzimidazole.

Properties of Compound (360):

^{1}H-NMR(DMSO-d6, δ): 2.56(3H, s), 5.56(2H, s), 7.22 (1H, d, J=7.9 Hz), 7.28(1H; dd, J=5.0 and 7.1 Hz), 7.45(1H, d, J=8.3 Hz), 7.74–7.79(2H, m), 7.95(1H, s), 8.48(1H, d, J=8.5 Hz).

EXAMPLE 297

Synthesis of 1-(butanesulfonylcarbamoyl)-2-methyl-1-(2-pyridylmethyl)benzimidazole (361)

In the same manner as in Example 98, 0.142 g of 1-(butanesulfonylcarbamoyl)-2-methyl-1-(2-pyridylmethyl) benzimidazole (361) were formed from 0.500 g of 6-carboxy-2-methyl-1-(2-pyridylmethyl)benzimidazole, 0.394 g of N,N'-carbonyldiimidazole, 0.334 g of 1-butanesulfonamide and 0.370 g of diazabicycloundecene.

Properties of Compound (361):

^{1}H-NMR(DMSO-d6, δ): 0.83(3H, t, J=7.3 Hz), 1.28–1.36 (2H, m), 1.52–1.58(2H, m), 2.55(3H, s), 3.06(2H, t, J=7.9 Hz), 5.56(2H, s), 7.17(1H, d, J=7.8 Hz), 7.29(1H, dd, J=4.2 and 7.3 Hz), 7.43(1H, d, J=8.4 Hz), 7.77(1H, dt, J=1.8 and 7.7 Hz), 7.81(1H, dd, J=1.4 and 8.4 Hz), 7.96(1H, s), 8.50(1H, d, J=4.7 Hz).

IR(Nujol): 1674 cm^{-1}.

mp: 139° C. (decomp.).

EXAMPLE 298

Synthesis of 6-ethoxycarbonyl-2-methyl-1-(4-nitrobenzyl)benzimidazole (362)

In the same manner as in Example 263, 0.51 g of 6-ethoxycarbonyl-2-methyl-1-(4-nitrobenzyl) benzimidazole (362) were formed from 0.67 g of ethyl 4-acetylamino-3-aminobenzoate, 0.39 g of sodium carbonate, 0.14 g of sodium iodide and 0.78 g of 4-nitrodibenzyl bromide.

Properties of Compound (362):

^{1}H-NMR($CDCl_3$, δ): 1.39(3H, t, J=7.1 Hz), 2.59(3H, s), 4.38(2H, q, J=7.1 Hz), 5.49(2H, s), 7.20(2H, d, J=8.6 Hz), 7.76(1H, d, J=8.5 Hz), 7.94(1H, d, J=1.1 Hz), 8.01(1H, dd, J=1.4 and 8.5 Hz), 8.20(2H, d, J=8.6 Hz).

EXAMPLE 299

Synthesis of 1-(4-aminobenzyl)-6-ethoxycarbonyl-2-methylbenzimidazole (363)

Six milliliters of ethanol and 0.8 ml of acetic acid were added to 0.50 g of 1-(4-nitrobenzyl)-6-ethoxycarbonyl-2-methylbenzimidazole and 0.47 g of reduced iron, and the mixture was refluxed for 4.5 hours. The reaction mixture was extracted with water and with ethyl acetate. The organic layer was washed with water, dried, and then concentrated under reduced pressure to give 0.46 g of 1-(4-aminobenzyl)-6-ethoxycarbonyl-2-methylbenzimidazole (363).

Properties of Compound (363):

^{1}H-NMR($CDCl_3$, δ): 1.40(3H, t, J=7.2 Hz), 2.59(3H, s), 4.38(2H, q, J=7.2 Hz), 5.25(2H, s), 6.61(2H, d, J=8.6 Hz), 6.87(2H, d, J=8.6 Hz), 7.71(1H, d, J=8.3 Hz), 7.96(1H, dd, J=1.5 and 8.4 Hz), 8.05(1H, d, J=1.3 Hz).

EXAMPLE 300

Synthesis of 1-[(4-benzoylamino)benzyl]-6-ethoxycarbonyl-2-methylbenzimidazole (364)

A solution of 0.25 g of benzoyl chloride in 4 ml of chloroform was added to a solution of 0.45 g of 1-(4-aminobenzyl)-6-ethoxycarbonyl-2-methylbenzimidazole and 0.15 g of pyridine in 8 ml of chloroform, and the mixture was stirred at room temperature for 16 hours. The reaction mixture was extracted with water and then with chloroform. The organic layer was concentrated under reduced pressure to give 0.33 g of 1-[(4-benzoylamino)benzyl]-6-ethoxycarbonyl-2-methylbenzimidazole (364).

Properties of Compound (364)

^{1}H-NMR($CDCl_3$, δ): 1.40(3H, t, J=7.1 Hz), 2.59(3H, s), 4.38(2H, q, J=7.1 Hz), 5.37(2H, s), 7.06(2H, d, J=8.5 Hz), 7.46–7.50(2H, m), 7.53–7.57(1H, m), 7.61(2H, d, J=8.5 Hz), 7.72(1H, d, J=8.4 Hz), 7.84–7.86(2H, m), 7.89(1H, br s), 7.98(1H, dd, J=1.5 and 8.5 Hz), 8.03(1H, s).

EXAMPLE 301

Synthesis of 1-[(4-benzoylamino)benzyl]-6-carboxy-2-methylbenzimidazole (365)

In the same manner as in Example 53, 0.28 g of 1-[(4-benzoylamino)benzyl]-6-carboxy-2-methylbenzimidazole (365) were formed from 0.31 g of 1-[(4-benzoylamino) benzyl]-6-ethoxycarbonyl-2-methylbenzimidazole.

Properties of the compound (365):

^{1}H-NMR(DMSO-d6, δ): 2.58(3H, s), 5.52(2H, s), 7.12 (2H, d, J=8.5 Hz), 7.48–7.52(2H, m), 7.54–7.58(1H, m), 7.61(1H, d, J=8.4 Hz), 7.73(2H, d, J=8.6 Hz), 7.79(1H, dd, J=1.5 and 8.4 Hz), 7.90–7.92(2H, m), 8.07(1H, d, J=1.2 Hz), 10.26(1H, s), 12.73(1H, br s).

EXAMPLE 302

Synthesis of 1-[(4-benzoylamino)benzyl]-6-(1-butanesulfonylcarbamoyl)-2-methylbenzimidazole (366)

In the same manner as in Example 98, 0.14 g of 1-[(4-benzoylamino)benzyl]-6-(1-butanesulfonylcarbamoyl)-2-methylbenzimidazole (366) were obtained from 0.26 g of 1-[(4-benzoylamino)benzyl]-6-carboxy-2-methylbenzimidazole, 0.17 g of N,N'-carbonyldiimidazole, 0.14 g of 1-butanesulfonamide and 0.16 g of diazabicycloundecene.

Properties of Compound (366):

^{1}H-NMR(DMSO-d6, δ): 0.85(3H, t, J=7.4 Hz), 1.40(2H, m), 1.68(2H, m), 2.56(3H, s), 3.52(2H, t, J=7.8 Hz), 5.50 (2H, s), 7.15(2H, d, J=8.6 Hz), 7.50(2H, t, J=7.5 Hz), 7.55–7.59(1H, m), 7.64(1H, d, J=8.5 Hz), 7.74(2H, d, J=8.6 Hz), 7.79(1H, dd, J=1.6 and 8.5 Hz), 7.90–7.92(2H, m), 8.24(1H, d, J=1.3 Hz), 10.27(1H, s), 11.92(1H, br s).

IR(Nujol): 1693 cm^{-1}.

mp: 267.5–268.1° C.

EXAMPLE 303

Synthesis of 6-ethoxycarbonyl-2-methyl-1-[4-(2-phenylethenyl)benzyl]benzimidazole (367)

In the same manner as in Example 263, 0.320 g of 6-ethoxycarbonyl-2-methyl-1-[4-(2-phenylethenyl)benzyl] benzimidazole (367) were formed from 0.405 g of ethyl 4-acetylamino-3-aminobenzoate, 0.253 g of potassium carbonate, 0.082 g of sodium iodide and 0.500 g of 4-chloromethylstilbene.

Properties of Compound (367):

^{1}H-NMR($CDCl_3$, δ): 1.40(3H, t, J=7.2 HJz), 2.6(3H, s), 4.38(2H, q, J=7.1 Hz), 5.38(2H, s), 7.01–7.09(4H, m),

7.26(1H, t, J=7.4 Hz), 7.35(2H, t, J=7.5 Hz), 7.45(2H, d, J=8.2 Hz), 7.49(2H, d, J=7.5 Hz), 7.73(1H, d, J=8.5 Hz), 7.99(1H, dd, J=1.5 and 8.4 Hz), 8.30(1H, d, J=1.2 Hz).

EXAMPLE 304

Synthesis of 6-ethoxycarbonyl-2-methyl-1-[4-(2-phenylethyl)benzyl]-benzimidazole (368)

Five-percent palladium on carbon was added to a solution of 0.320 g of 6-ethoxycarbonyl-2-methyl-1-[4-(2-phenylethenyl)benzyl]benzimidazole in 10 ml of ethanol in a nitrogen atmosphere, and the mixture was stirred in a hydrogen atmosphere for 23 hours. The solid material was separated through filtration, and the filtrate was concentrated to give 6-ethoxycarbonyl-2-methyl-1-[4-(2-phenylethyl) benzyl]benzimidazole (368). This compound was used in the subsequent reaction at once.

EXAMPLE 305

Synthesis of 6-carboxy-2-methyl-1-[4-(2-phenylethyl)benzyl]benzimidazole (369)

In the same manner as in Example 53, 0.242 g of 6-carboxy-2-methyl-1-[4-(2-phenylethyl)benzyl]-benzimidazole (369) were formed from 0.283 g of 6-ethoxycarbonyl-2-methyl-1-[4-(2-phenylethyl)benzyl]-benzimidazole.

Properties of Compound (369)

^{1}H-NMR(DMSO-d6, δ): 2.56(3H, s), 2.82(4H, s), 5.51 (2H, s), 7.02(2H, d, J=8.1 Hz), 7.11–7.27(7H, m), 7.61(1H, d, J=8.4 Hz), 7.78(1H, dd, J=1.5 and 8.04(1H, s), 12.72(1H, s).

EXAMPLE 306

Synthesis of 6-(1-butanesulfonylcarbamoyl)-2-methyl-[4-(2-phenylethyl)benzyl]benzimidazole (370)

In the same manner as in Example 98, 0.249 g of 6-(1-butanesulfonylcarbamoyl)-2-methyl-[4-(2-phenylethyl)benzyl]benzimidazole (370) were formed from 0.225 g of 6-carboxy-2-methyl-1-[4-(2-phenylethyl) benzyl]-benzimidazole, 1.214 g of N,N'-carbonyldiimidazole, 0.167 g of 1-butanesulfonamide and 0.185 g of diazabicycloundecene.

Properties of Compound (370):

^{1}H-NMR(DMSO-d6, δ): 0.86(3H, t, J=7.4 Hz), 1.35–1.42 (2H, m), 1.63–1.71(2H, m), 2.53(3H, s), 2.83(4H, s), 3.52 (2H, t, J=7.7 Hz), 5.49(2H, s), 7.04(2H, d, J=8.0 Hz), 7.12–7.25(7H, m), 7.64(1H, d, J=8.4 Hz), 7.79(1H, dd, J=1.7 and 8.5 Hz), 8.22(1H, d, J=1.3 Hz), 11.92(1H, s).

IR(Nujol): 1682 cm^{-1}.

mp: 95.4–99.0° C.

PRODUCTION EXAMPLE 60

Production of 4-benzoylbenzyl bromide

In the same manner as in Production Example 48, 5.28 g of 4-benzoylbenzyl bromide were formed from 3.92 g of 4-methylbenzophenone, 4.28 g of N-bromosuccinimide and 0.40 g of 2,2'-azobisisobutylonitrile.

Properties of the compound:

^{1}H-NMR($CDCl_3$, δ): 4.54(2H, s), 7.47–7.52(4H, m), 7.58–7.62(1H, m), 7.77–7.82(4H, m).

EXAMPLE 307

Synthesis of 1-[(4-benzoyl)benzyl]-6-ethoxycarbonyl-2-methylbenzimidazole (371)

In the same manner as in Example 263, 0.70 g of 1-[(4-benzoyl)benzyl]-6-ethoxycarbonyl-2-methylbenzimidazole (371) were formed from 0.56 g of ethyl 4-acetylamino-3-aminobenzoate, 0.33 g of sodium carbonate, 0.11 g of sodium iodide and 0.83 g of 4-benzoylbenzyl bromide.

Properties of Compound (371):

^{1}H-NMR($CDCl_3$, δ): 1.40(3H, t, J=7.2 Hz), 2.61(3H, s), 4.39(2H, q, J=7.2 Hz), 5.47(2H, s), 7.14(2H, d, J=8.2 Hz), 7.45–7.48(2H, m), 7.56–7.60(1H, m), 7.74–7.77(5H, m), 7.99–8.02(2H, m).

EXAMPLE 308

Synthesis of 1-[(4-benzoyl)benzyl]-6-carboxy-2-methylbenzimidazole (372)

In the same manner as in Example 53, 0.55 g of 1-[(4-benzoyl)benzyl]-6-carboxy-2-methylbenzimidazole (372) were formed from 0.68 g of 1-[(4-benzoyl)benzyl]-6-ethoxycarbonyl]-2-methylbenzimidazole.

Properties of Compound (372):

^{1}H-NMR(DMSO-d6, δ): 2.57(3H, s), 5.71(2H, s), 7.25 (2H, d, J=8.2 Hz), 7.52(2H, t, J=7.7 Hz), 7.62–7.66(2H, m), 7.68–7.72(4H, m), 7.80(1H, dd, J=1.3 and 8.4 Hz), 8.08(1H, d, J=1.1 Hz), 12.72(1H, br s).

EXAMPLE 309

Synthesis of 1-[(4-benzoyl)benzyl]-6-(1-butanesulfonylcarbamoyl)-2-methylbenzimidazole (373)

In the same manner as in Example 98, 0.13 g of 1-[(4-benzoyl)benzyl]-6-(1-butanesulfonylcarbamoyl)-2-methylbenzimidazole (373) were formed from 0.52 g of 1-[(4-benzoyl)benzyl]-6-carboxy-2-methylbenzimidazole, 0.34 g of N,N'-carbonyldiimidazole, 0.29 g of 1-butanesulfonamide and 0.32 g of diazabicycloundecene.

Properties of Compound (373):

^{1}H-NMR(DMSO-d6, δ): 0.84(3H, t, J=7.4 Hz), 1.38(2H, m), 1.66(2H, m), 2.54(3H, s), 3.48(2H, t, J=7.7 Hz), 5.67 (2H, s), 7.27(2H, d, J=8.2 Hz), 7.51–7.55(2H, m), 7.63–7.73 (6H, m), 7.81(1H, dd, J=1.6 and 8.5 Hz), 8.21(1H, d, J=1.4 Hz).

IR(Nujol): 1660 cm^{-1}.

mp: 111.0–112.4° C.

Mass(FAB): m/e 490(M+1).

EXAMPLE 310

Synthesis of 6-carboxy-2-methyl-[4-(2-phenylethenyl)benzyl]benzimidazole (374)

In the same manner as in Example 53, 0.237 g of 6-carboxy-2-methyl-[4-(2-phenylethenyl)benzyl] benzimidazole (374) were formed from 0.500 g of 6-ethoxycarbonyl-2-methyl-1-[4-(2-phenylethenyl)benzyl] benzimidazole.

Properties of Compound (374):

^{1}H-NMR(DMSO-d6, δ): 2.59(3H, s), 5.58(2H, s), 7.12 (2H, d, J=8.2 Hz), 7.21(2H, s), 7.26(1H, t, J=7.4 Hz), 7.36(2H, t, J=7.6 Hz), 7.57(4H, d, J=8.0 Hz), 7.62(1H, d,

J=8.4 Hz), 7.79(1H, dd, J=1.5 and 8.4 Hz), 8.07(1H, d, J=1.2 Hz), 12.73(1H, s).

EXAMPLE 311

Synthesis of 6-(1-butanesulfonylcarbamoyl)-2-methyl-[4-(2 -phenylethenyl)benzyl]benzimidazole (375)

In the same manner as in Example 98, 0.239 g of 6-(1-butanesulfonylcarbamoyl)-2-methyl-[4-(2-phenylethenyl)benzyl]benzimidazole (375) were formed from 0.237 g of 6-carboxy-2-methyl-[4-(2-phenylethenyl) benzyl]benzimidazole, 0.209 g of N,N'-carbonyldiimidazole, 0.176 g of 1-butanesulfonamide and 0.195 g of diazabicycloundecene.

Properties of Compound (375):

^{1}H-NMR(DMSO-d6, δ): 0.86(3H, t, J=7.4 Hz), 1.35–1.43 (2H, m), 1.63–1.70(2H, m), 2.56(3H, s), 3.52(2H, t, J=7.6 Hz), 5.55(2H, s), 7.15(2H, d, J=8.2 Hz), 7.22(2H, s), 7.26 (1H, t, J=7.4 Hz), 7.36(2H, t, J=7.6 Hz), 7.57(1H, d, J=7.3 Hz), 7.58(1H, d, J=8.2 Hz), 7.66(1H, d, J=8.5 Hz), 7.80(1H, d, J=8.4 Hz), 8.24(1H, s), 11.93(1H, brs).

IR(Nujol): 1680 cm^{-1}.

mp: 140.3–143.4° C.

EXAMPLE 312

Synthesis of 1-(dibenzofuran-2-ylmethyl)-6-ethoxycarbonyl-2-methylbenzimidazole (376)

In the same manner as in Example 263, 0.47 g of 1-(dibenzofuran-2-ylmethyl)-6-ethoxycarbonyl-2-methylbenzimidazole (376) were formed from 0.480 g of ethyl 4-acetylamino-3-aminobenzoate, 0.274 g of sodium carbonate, 0.097 g of sodium iodide and 0.56 g of 2-bromomethyldibenzofuran.

Properties of Compound (376):

^{1}H-NMR($CDCl_3$, δ): 1.38(3H, t, J=7.1 Hz), 2.62(3H, s), 4.36(2H, q, J=7.1 Hz), 5.54(2H, s), 7.19(1H, dd, J=1.6 and 8.5 Hz), 7.32(1H, t, J=7.6 Hz), 7.43–7.59(4H, m), 7.76(1H, d, J=8.4 Hz), 7.85(1H, d, J=7.1 Hz), 8.00(1H, dd, J=1.3 and 8.4 Hz), 8.07(1H, d, J=1.2 Hz).

EXAMPLE 313

Synthesis of 6-carboxy-1-(dibenzofuran-2-ylmethyl)-2-methylbenzimidazole (377)

In the same manner as in Example 53, 0.336 g of 6-carboxy-1-(dibenzofuran-2-ylmethyl)-2-methylbenzimidazole (377) were formed from 0.46 g of 6-ethoxycarbonyl-2-methylbenzimidazole.

Properties of Compound (377):

^{1}H-NMR(DMSO-d6, δ): 2.63(3H, s), 5.71(2H, s), 7.27 (1H, d, J=8.5 Hz), 7.36(1H, t, J=7.5 Hz), 7.50(1H, t), 7.61–7.68(3H, m), 7.78(1H, d, J=8.3 Hz), 7.97(1H, s), 7.07–8.11(2H, m).

EXAMPLE 314

Synthesis of 1-(dibenzofuran-2-ylmethyl)-6-(1-butanesulfonylcarbamoyl)-2-methylbenzimidazole (378)

In the same manner as in Example 98, 0.249 g of 1-(dibenzofuran-2-ylmethyl)-6-(1-butanesulfonylcarbamoyl)-2-methylbenzimidazole (378) were formed from 0.255 g of 6-carboxy-1-(dibenzofuran-2-ylmethyl)-2-methylbenzimidazole, 0.197 g of N,N'-carbonyldiimidazole, 0.167 g of 1-butanesulfonamide and 0.185 g of diazabicycloundecene.

Properties of Compound (378):

^{1}H-NMR(DMSO-d6, δ): 0.81(3H, t, J=7.4 Hz), 1.36(2H, m), 1.65(2H, m), 2.60(3H, s), 3.50(2H, t, J=7.7 Hz), 5.69 (2H, s), 7.29(1H, dd, J=1.96 and 8.7 Hz), 7.34–7.38(1H, m), 7.48–7.52(1H, m), 7.63–7.68(3H, m), 7.81(1H, dd, J=1.7 and 8.5 Hz), 8.00(1H, d, J=1.4 Hz), 8.94(1H, d, J=7.1 Hz), 8.28(1H, d, J=1.4 Hz), 12.70(1H, br s).

IR(Nujol): 1682 cm^{-1}.

mp: 224.1–229.8° C.

PRODUCTION EXAMPLE 61

Production of N-1-butanesulfonyl-3-acetylamino-4-nitrobenzamide

In the same manner as in Production Example 28, 6.30 g of N-1-butanesulfonyl-3-acetylamino-4-nitrobenzamide were obtained from 5.15 g of 3-acetylamino-4-nitrobenzoic acid, 5.59 g of N,N'-carbonyldiimidazole, 4.73 g of 1-butanesulfonamide and 5.25 g of diazabicycloundecene.

Properties of the compound:

^{1}H-NMR(DMSO-d6, δ): 0.87(3H, t, J=7.4 Hz), 1.40(2H, m), 1.68(2H, m), 2.07(3H, s), 3.51(2H, t), 7.83(1H, dd, J=1.8 and 8.5 Hz), 8.03(1H, d, J=8.5 Hz), 8.07(1H, d, J=1.8 Hz), 10.43(1H, s), 12.64(1H, br s).

PRODUCTION EXAMPLE 62

Production of N-1-butanesulfonyl-3-amino-4-nitrobenzamide

A mixture containing 6.30 g of N-1-butanesulfonyl-3 -acetylamino-4-nitrobenzamide, a 10% sodium hydroxide aqueous solution, 300 ml of ethanol and 200 ml of water was stirred at room temperature for 4 hours and then at 50° C. for 3 hours. The solvent was distilled off to approximately a half volume, and the residue was adjusted to a pH of 2 with 10% hydrochloric acid. The crystals precipitated were collected, and were dried under reduced pressure to give 5.22 g of N-1-butanesulfonyl-3-amino-4-nitrobenzamide.

Properties of the compound:

^{1}H-NMR(DMSO-d6, δ): 0.87(3H, t, J=7.4 Hz), 1.40(2H, m), 1.66(2H, m), 3.49(2H, m), 6.99(1H, dd, J=1.8 and 9.0 Hz), 7.49(1H, d, J=1.8 Hz), 7.55(2H, br s), 8.04(1H, d, J=9.0 Hz), 12.28(1H, br s).

PRODUCTION EXAMPLE 63

Production of N-1-butanesulfonyl-3-(2,4-dichlorobenzylamino)-4-nitrobenzamide

A solution containing 1.10 g of N-1-butanesulfonyl-3-amino-4-nitrobenzamide, 0.273 g of sodium iodide, 1.54 g of potassium carbonate, 2.17 g of 2,4-dichlorobenzyl chloride and 10 ml of methanol was stirred at 60° C. for 24 hours. Further, 2.00 g of 2,4-dichlorobenzyl chloride were added thereto, and the mixture was heated at 60° C. for 36 hours. To the reaction solution were added ethyl acetate and a saturated aqueous solution of sodium hydrogencarbonate, and N-1-butanesulfonyl-3-(2,4-dichlorobenzylamino)-4-nitrobenzamide was extracted in the aqueous layer. The organic layer was concentrated to give 0.885 g of N-1-butanesulfonyl-3-(2,4-dichlorobenzylamino)-4-nitrobenzamide.

Properties of the compound:

^{1}H-NMR(DMSO-d6, δ): 0.81(3H, t, J=7.3 Hz), 1.29(2H, m), 1.49(2H, m), 2.97(2H, m), 4.66(2H, d, J=6.0 Hz), 7.22(1H, d, J=8.9 Hz), 7.27(1H, s), 7.31(1H, d, J=8.4 Hz), 7.37(1H, d, J=8.3 Hz), 7.65(1H, s), 8.04(1H, d, J=8.9 Hz), 8.57(1H, t).

PRODUCTION EXAMPLE 64

Production of N-1-butanesulfonyl-4-amino-3-(2,4-dichlorobenzylamino)benzamide

N-1-butanesulfonyl-3-(2,4-dichlorobenzylamino)-4-nitrobenzamide (0.505 g) was added to a mixture of 1.32 g of sodium hydrosulfite, 1 ml of ethanol, 1 ml of tetrahydrofuran and 1 ml of water at room temperature. The mixture was heat-refluxed for 40 minutes. The solvent was distilled off under reduced pressure, and water was added to the residue. The solid material precipitated was collected, and was dried. Further, the resulting material was washed with a mixed solution of 10 ml of methanol and 3 ml of water, and was dried to give 0.220 g of N-1-butanesulfonyl-4-amino-3-(2,4-dichlorobenzylamino)benzamide.

Properties of the compound:

^{1}H-NMR(DMSO-d6, δ): 0.93(3H, t, J=7.4 Hz), 1.45(2H, m), 1.83(2H, m), 3.57(2H, m), 5.45(2H, s), 6.36(1H, d, J=8.2 Hz), 7.11(1H, d, J=8.3 Hz), 7.51(1H, s), 7.75(1H, d), 7.79(1H, d), 7.88(1H, s).

EXAMPLE 315

Synthesis of 6-(1-butanesulfonylcarbamoyl)-1-(2,4-dichlorobenzyl)-2-hydroxybenzimidazole (379)

A mixture of 0.220 mg of N-1-butanesulfonyl-4-amino-3-(2,4-dichlorobenzylamino)benzamide, 0.3 ml of tetramethoxymethane and 2.0 ml of acetic acid was stirred at 60° C. for 4 hours. Acetic acid was distilled off under reduced pressure, and the residue was extracted with chloroform and with water. The chloroform layer was concentrated, and 4.0 ml of methanol and 36% hydrochloric acid (4 drops). were added to the residue. The mixture was stirred at 60° C. for 2 hours. The reaction solution was neutralized with a saturated aqueous solution of sodium hydrogencarbonate. The crystals precipitated were washed with water, and were dried to give 0.207 g of 6-(1-butanesulfonylcarbamoyl)-1-(2,4-dichlorobenzyl)-2-hydroxybenzimidazole (379).

Properties of Compound (379):

^{1}H-NMR(DMSO-d6, δ): 0.83(3H, t, J=7.3 Hz), 1.36(2H, m), 1.61(2H, m), 3.40(2H, m), 5.08(2H, s), 6.94(1H, d, J=8.3 Hz), 7.11(1H, d, J=8.2 Hz), 7.36(1H, dd, J=2.0 and 8.4 Hz), 7.58(1H, s), 7.68–7.73(2H, m), 11.47(1H, br s), 11.77 (1H, br s).

IR(Nujol): 1689 cm^{-1}.

mp: 254–256° C.

Mass(FD): m/e 455(M).

EXAMPLE 316

Synthesis of 6-ethoxycarbonyl-2-methyl-1-(2-quinolylmethyl)benzimidazole (380)

In accordance with Example 263, 0.87 g of 6-ethoxycarbonyl-2-methyl-1-(2-quinolylmethyl) benzimidazole (380) were formed from 2.22 g of ethyl 4-acetylamino-3-aminobenzoate, 1.27 g of sodium carbonate, 0.45 g of sodium iodide and 2.28 g of 2-bromomethylquinoline.

Properties of the compound (380):

^{1}H-NMR(DMSO-d6, δ): 1.27(3H, t, J=7.1 Hz), 2.62(3H, s), 4.26(2H, q, J=7.1 Hz), 5.85(2H, s), 7.35(1H, d, J=8.5 Hz), 7.58(1H, m), 7.63(1H, d, J=8.4 Hz), 7.73(1H, m), 7.78(1H, dd, J=1.3 and 8.4 Hz), 7.86(1H, d, J=8.4 Hz), 7.95(1H, d, J=8.0 Hz), 8.14(1H, s), 8.36(1H, d, J=8.5 Hz).

EXAMPLE 317

Synthesis of 6-carboxy-2-methyl-(2-quinolylmethyl) benzimidazole (381)

In the same manner as in Example 53, 0.46 g of 6-carboxy-2-methyl-(2-quinolylmethyl)benzimidazole (381) were formed from 0.85 g of 6-ethoxycarbonyl-2-methyl-1-(2-quinolylmethyl)benzimidazole.

Properties of Compound (381):

^{1}H-NMR(DMSO-d6, δ): 2.62(3H, s), 5.83(2H, s), 7.35 (1H, d, J=8.5 Hz), 7.57(1H, m), 7.60(1H, d, J=8.5 Hz), 7.72(1H, t, J=7.6 Hz), 7.77(1H, d, J=8.4 Hz), 7.86(1H, d, J=8.4 Hz), 7.94(1H, d, J=8.1 Hz), 8.11(1H, s), 8.35(1H, d, J=8.5 Hz).

EXAMPLE 318

Synthesis of 6-(1-butanesulfonylcarbamoyl)-2-methyl-1-(2-quinolylmethyl)benzimidazole (382)

In the same manner as in Example 98, 0.088 g of 6-(1-butanesulfonylcarbamoyl)-2-methyl-1-(2-quinolylmethyl)benzimidazole (382) were formed from 0.222 g of 6-carboxy-2 -methyl-1-(2-quinolylmethyl) benzimidazole, 0.195 g of N,N'-carbonyldiimidazole, 0.165 g of 1-butanesulfonamide and 0.183 g of diazabicycloundecene.

Properties of Compound (382):

^{1}H-NMR(DMSO-d6, δ): 0.82(3H, t, J=7.3 Hz), 1.36(2H, m), 1.64(2H, m), 2.61(3H, s), 3.48(2H, t, J=7.4 Hz), 5.82 (2H,s), 7.32(1H,d, J=8.5 Hz), 7.58(1H, m), 7.65(1H, d, J=8.5 Hz), 7.73(1H, t, J=7.6 Hz), 7.78(1H, m), 7.87(1H, d, J=8.5 Hz), 7.95(1H,d, J=8.1 Hz), 8.23(1H, s), 8.37(1H, d, J=8.5 Hz), 11.86(1H,brs).

IR(Nujol): 1684 cm^{-1}.

mp: 185.5–187.5° C.

PRODUCTION EXAMPLE 65

Production of ethyl 4-amino-3-(2,4-dichlorobenzylamino)benzoate

Crude ethyl 4-amino-3-(2,4-dichlorobenzylamino) benzoate was formed from 1.40 g of 3-(2,4-dichlorobenzylamino)-4-nitrobenzoate and 4.50 g of sodium hydrosulfite in the same manner as in Production Example 64. This compound was used in the subsequent reaction at once.

EXAMPLE 319

Synthesis of 1-(2,4-dichlorobenzylamino)-2-hydroxy-6-ethoxycarbonylbenzimidazole (383)

In the same manner as in Example 315, 0.400 g of 1-(2,4-dichlorobenzylamino)-2-hydroxy-6-ethoxycarbonylbenzimidazole (383) were formed from ethyl 4-amino-3-(2,4-dichlorobenzylamino)benzoate obtained in the above-mentioned Production Example 63 and 2.60 g of tetramethoxymethane.

Properties of Compound (383):

^{1}H-NMR(DMSO-d6, δ): 1.27(3H, t, J=7.1 Hz), 4.24(2H, q, J=7.1 Hz), 5.12(2H, s), 7.04(1H, d, J=8.4 Hz), 7.12(1H, d, J=8.2 Hz), 7.37(1H, dd, J=2.1 and 8.4 Hz), 7.51(1H, s), 7.67–7.72(2H, m), 11.37(1H, br s).

EXAMPLE 320

Synthesis of 6-ethoxycarbonyl-2-methyl-1-[3-(4-bromoisoquinolyl)methyl]benzimidazole (384)

In the same manner as in Example 263, 0.30 g of 6-ethoxycarbonyl-2-methyl-1-[3-(4-bromoisoquinolyl)methyl]benzimidazole (384) were formed from 0.87 g of ethyl 4-acetylamino-3-aminobenzoate, 0.53 g of sodium carbonate, 0.18 g of sodium iodide and 0.87 g of 4-bromo-3-bromomethylisoquinoline.

Properties of Compound (384):

^{1}H-NMR(DMSO-d6, δ): 1.26(3H, t, J=7.0 Hz), 2.59(3H, s), 4.24(2H, q, J=7.0 Hz), 5.93(2H, s), 7.61(1H, d, J=8.4 Hz), 7.75–7.80(2H, m). 7.99(1H, m), 8.03(1H, s), 8.13(1H, d, J=8.1 Hz), 8.23(1H, d, J=8.5 Hz), 9.12(1H, s).

EXAMPLE 321

Synthesis of 6-carboxy-2-methyl-[3-(4-bromoisoquinolyl)methyl]benzimidazole (385)

In the same manner as in Example 53, 0.118 g of 6-carboxy-2-methyl-[3-(4-bromoisoquinolyl)methyl]benzimidazole (385) were formed from 0.290 g of 6-ethoxycarbonyl-2-methyl-1-[3-(4-bromoisoquinolyl)methyl]benzimidazole. This compound was used in the subsequent reaction at once.

EXAMPLE 322

Synthesis of 6-(1-butanesulfonylcarbamoyl)-2-methyl-1-[3-(4-bromoisoquinolyl)methyl]benzimidazole (386)

In the same manner as in Example 98, 0.075 g of 6-(1-butanesulfonylcarbamoyl)-2-methyl-1-[3-(4-bromoisoquinolyl)methyl]benzimidazole (386) were formed from 0.111 g of 6-carboxy-2-methyl-1-[3-(4-bromoisoquinolyl)-methyl]benzimidazole, 0.097 g of N,N'-carbonyldiimidazole, 0.082 g of 1-butanesulfonamide and 0.091 g of diazabicycloundecene.

Properties of Compound (386):

^{1}H-NMR(DMSO-d6, δ): 0.81(3H, t, J=7.4 Hz), 1.35(2H, m), 1.62(2H, m), 2.54(3H, s), 3.46(2H, t, J=7.5 Hz), 5.91 (2H, s), 7.63(1H, d, J=8.5 Hz), 7.76(1H, dd, J=8.5 and 1.4 Hz), 7.79(1H, t, J=7.6 Hz), 8.00(1H, t, J=7.9 Hz), 8.08(1H, t, J=1.1Hz), 8.13(1H, d, J=8.2 Hz), 8.24(1H, d, J=8.5 Hz), 9.11(1H,s), 11.81(1H, brs).

IR(Nujol): 1678 cm^{-1}.

mp: 258–259° C.

Mass(FAB): m/e 515, 517(M+1).

From among the compounds of the present invention, the typical compounds were selected, and were tested for pharmacological properties.

TEST EXAMPLE 1

Stimulatory activity of triglyceride (TG) accumulation in 3T3-L1 cells (pre-adipocytes).

Test Compound

6-benzylsulfonylcarbamoyl-2-cyclopropyl-1-(2-fluorobenzyl)benzimidazole

Devices Used

1. Centrifuge: TOMY LC-122
2. Incubator: ESPEC BNA-121D
3. Mixer: Automatic Labo-Mixer
4. Water bath: TAITEC PERSONAL-11
5. Spectrophotometer: Shimadzu UV Visible Spectrophotometer UV-160A
6. 24-well plate: IWAKI GLASS CORNING

Reagents Used

1. Medium: Dulbecco minimum essential medium (MEM)+5% fetal calf serum (FCS)
2. PBS (–): solution having the following composition

NaCl	0.8 g/liter
KCl	0.2
Na_2HPO_4	1.15
KH_2PO_4	0.2

3. Solution of EDTA and trypsin: 0.02% EDTA+0.25% trypsin/PBS(–)
4. Dexamethasone: made by Sigma
5. IBMX (3-isobutyl-1-methylxanthine): made by Sigma
6. Insulin: made by Sigma
7. DMSO (dimethylsulfoxide): made by Wako Pure Chemical Industries, Ltd.
8. TG measuring kit: Triglyceride-Test Wako (acetyl-acetone method): made by Wako Pure Chemical Industries, Ltd.
9. 0.1-N NaOH solution: prepared by diluting a iN NaOH solution to 10 times with distilled water.
10. Bio-Rad Protein Assay Reagent: made by Bio-Rad.
11. Bovine albumin: made by Sigma

Test Method

Preparation of 3T3-L1 Cells

3T3-L1 cells just before a confluent state were prepared in an F75 flask. The medium was removed, and the residue was washed twice with 5 ml of PBS (–). The cells were detached using a solution of EDTA and trypsin. Ten milliliters of the medium were added thereto to form a suspension. This suspension was collected in a 50-milliliter centrifuge tube, and was subjected to centrifugation at 1,000 rpm for 5 minutes. Thus, the cells were precipitated, and the supernatant was removed. The cells were re-suspended in 20 ml of the medium, and the number of cells was counted. The suspension was adjusted such that the concentration of the cells reached 6×10^4 cells/ml, and was inoculated into a 24-well plate in an amount of 1 ml/well. In this state, the incubation was conducted in an incubator at 37° C. in 5% CO_2 for 2 days.

Preparation and Addition of Dexamethasone and IBMX

A solution of 1-mM dexamethasone and 500-mM IBMX was prepared in DMSO. Further, this solution was diluted to 1,000 times with the medium to form a solution of 1 μM dexamethasone and 0.5 mM IBMX. At the same time, DMSO was diluted with the medium to form a 0.1% DMSO solution as well.

Subsequently, the 24-well plate containing the incubated 3T3-L1 cells was withdrawn from the incubator. It was identified using a microscope that the cells became confluent, and the medium was removed through suction. The 2 wells of the 24-well plate were charged with the 0.1% DMSO solution in an amount of 1 ml/well, and the remaining 22 wells were charged with the solution of 1-μM dexamethasone and 0.5 mM IBMX in an amount of 1

ml/well. In this state, the incubation was conducted in an incubator at 37° C. in 5% CO_2 for 1 day.

Preparation and Addition of a Test Chemical Agent and Insulin

A test chemical agent was diluted with DMSO to 1×10^{-2} M, 1×10^{-3} M and 1×10^{-4} M. The dilute solutions were further diluted to 500 times, and were adjusted to 2×10^{-5} M, 2×10^{-6} M and 2×10^{-7} M respectively. At the same time, a 0.2% DMSO solution was also prepared. Insulin which had been adjusted to 100 μM (in 0.2% bovine serum albumin (BSA) and 3-mM HCl) and had been stored at −80° C. was naturally thawed, diluted to 50,000 times with the medium, and adjusted to 2-nM.

Subsequently, the 24-well plate to which dexamethasone and IBMX had been added the preceding day was withdrawn from the incubator. It was identified using a microscope that the shape of the cells was changed with the addition of dexamethasone and IBMX. Then, the medium was removed through suction. The 2 wells to which the 0.1% DMSO solution had been added the preceding day were charged with the 0.2% DMSO solution in an amount of 500 μl/well and the medium (this was required to check the cell state at that time). The remaining 22 wells (containing the solution of dexamethasone and IBMX) were charged with the 0.2% DMSO solution (2 wells). or the test chemical agent (20 wells). in an amount of 500 μl/well and then with the insulin solution in an amount of 500 μl/well. In this state, the incubation was conducted in an incubator at 37° C. in 5% CO_2 for from 4 to 5 days.

Measurement of Triglyceride (TG) and Protein

Four to five days after the addition of the test chemical agent and the insulin solution, the 24-well plate was withdrawn from the incubator. The medium was discarded by decantation, and the remaining medium was then absorbed in a paper towel to completely remove the medium. Subsequently, the residue was extracted twice with isopropyl alcohol, and TG was measured at a wavelength of 410 nm using a TG-measuring kit (acetyl-acetone method). Subsequently, isopropyl alcohol was completely vaporized from the plate in which the extraction with isopropyl alcohol was completed. This plate was then charged with a 0.1-N NaOH solution in an amount of 400 μl/well, and was allowed to stand at room temperature for 30 minutes to dissolve the cells. This solution was sampled into a tube in an amount of 50 μl. Further, a solution obtained by diluting a Bio-Rad protein assay reagent to 5 times with distilled water was added to the tube in an amount of 2.5 ml. The mixture was stirred well, and protein was measured at a measurement wavelength of 595 nm using a spectrophotometer.

Results

The stimulatory activity of the test compound for TG accumulation was calculated, when 1×10^{-5} M of a control compound, pioglitazone, was defined as 100% and insulin (+) without the chemical agent was defined as 0%. The result is shown following.

TABLE 1

Concentration (M)	Stimulatory activity of TG accumulation (%)
1×10^{-5}	38.2%

TEST EXAMPLE 2

Test for activity of decreasing plasma glucose using db/db mice

Test Compounds

6-benzenesulfonylcarbamoyl-2-cyclopropyl-1-(2-fluorobenzyl)benzimidazole (177)

6-benzenesulfonylcarbamoyl-1-(2-chlorobenzyl)-2-methylbenzimidazole (163)

1-(biphenyl-4-ylmethyl)-6-(1-butanesulfonylcarbamoyl)-2-methylbenzimidazole (172)

Animal Used

Five-week-old female mice [C57BL/KsJ-dbm db+/db+, C57BL/KsJ-dbm +m/+m (Jackson Laboratory) were purchased, and were kept for 2 to 3 weeks. Then, these mice were used in the test.

Preparation of an Agent

A test compound was mixed with a powdered chow (CE-2, made by Nippon Clea) using a mortar. According to the amount of food intake of the mouse, the mixing ratios, 0.1%, 0.03%, and 0.01% corresponded to 100, 30, and 10 mg/kg body weight, respectively. The mixed chow was changed twice a week. The feed amount and the remaining amount were recorded, and the intake was calculated from the difference therebetween.

Test Schedule

The female db/db mice were grouped according to the body weight, the plasma glucose and the plasma triglyceride concentrations. Then, the mixture containing the test compound was administered to the mice for 14 days (from 8 to 10 weeks old). In the morning on day 7 and day 14, the blood was collected from the orbital venous plexus using heparinized glass capillary tubes (Chase Heparinized Capillary Tubes), and a plasma fraction was obtained through centrifugal separation. Plasma glucose, triglyceride, and insulin concentrations were measured on day 0 and day 14 as well as plasma glucose and triglyceride concentrations on day 7. The body weight was measured on day 0, day 7, and day 14. After the final collection of the blood, the mice were killed using CO_2 gas.

Measurement Method

The plasma glucose was measured by a glucose oxidase method (Glucose CII-Test Wako made by Wako Pure Chemical Industries, Ltd.) using from 10 to 15 μl of plasma. The plasma triglyceride concentration was measured by a GPO-p-chlorophenol method (Triglyceride G-Test Wako made by Wako Pure Chemical Industries, Ltd.) or a GPO-DAOS method (Triglyceride E-Test Wako) using from 10 to 15 μl of plasma. The above-mentioned measurements were conducted immediately after the blood collection. The plasma insulin concentration was measured by radio immuno assay method (Phadesef Insulin RIA Kit made by Cabi Pharmacia) using 20 μl of plasma (which can be stored at −20° C.).

Results

The difference in the plasma glucose and the plasma triglyceride concentrations between the db/db mouse and the +/+ mouse was defined as 100%, and the rate (%) of decrease in the plasma glucose and the plasma triglyceride concentrations of the group to which the test compound was administered was calculated. The results were shown in Table 2.

TABLE 2

Compound No.	Dose (mg/kg)	Activity of decreasing plasma glucose (%)
(177)	30	34.5
(163)	30	72
(172)	10	70–80

INDUSTRIAL APPLICABILITY

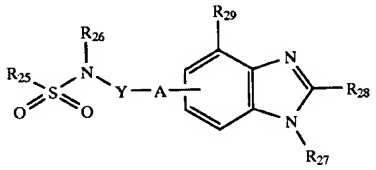
Herein provided are novel benzimidazole derivatives and their pharmaceutically acceptable salts. These compounds and their salts have blood sugar level-depressing activity or

PDE5-inhibiting activity, and are useful for preventing and treating impaired glucose tolerance, diabetes (type II diabetes), diabetic complications such as diabetic nephropathy, diabetic neuropathy and diabetic retinopathy, syndrome of insulin resistance (e.g., insulin receptor disorders, Rabson-Mendenhall syndrome, leprechaunism, Kobberling-Dunnigan syndrome, Seip syndrome, Lawrence syndrome, Cushing syndrome, acromegaly, etc.), hyperlipidemia, atherosclerosis, cardiovascular disorders (e.g., stenocardia, cardiac failure, etc.), hyperglycemia(e.g., abnormal-saccharometabolism such as feeding disorders, etc.), or hypertension; or stenocardia, hypertension, pulmonary hypertension, congestive heart failure, glomerulopathy (e.g., diabetic glomerulosclerosis, etc.), tubulointerstitial disorders (e.g., renopathy induced by FK506, cyclosporin, etc.), renal failure, atherosclerosis, angiostenosis (e.g., after percutaneous arterioplasty), distal angiopathy, cerebral apoplexy, chronic reversible obstructions (e.g., bronchitis, asthma (chronic asthma, allergic asthma), etc.), allergic rhinitis, urticaria, glaucoma, diseases characterized by enteromotility disorders (e.g., hypersensitive enteropathy syndrome, etc.), impotence (e.g., organic impotence, psychic impotence, etc.), and diabetic complications (e.g., diabetic gangrene, diabetic arthropathy, diabetic glomerulosclerosis, diabetic dermatopathy, diabetic neuropathy, diabetic cataract, diabetic retinopathy, etc.), nephritis, cancerous cachexia, or restenosis after PTCA.

We claim:

1. A benzimidazole derivative of the following formula, or its pharmaceutically acceptable salt:

(IX)



wherein R_{27} represents a hydrogen atom, an alkyl group having up to 7 carbon atoms, a halo-lower alkyl group, an arylsulfonyl group, an aryl-lower alkyl group, a quinolyl-lower alkyl group, an isoquinolyl-lower alkyl group, a halo-quinolyl-lower alkyl group, or a halo-isoquinolyl-lower alkyl group; the aromatic ring moiety in said aryl-lower alkyl group may be substituted by one or two substituents selected from the group consisting of a halogen atom, a lower alkyl group, a halo-lower alkyl group, a cyanoaryl group, an amino group, a lower alkoxy group, a nitro group, a cyano group, an aryl group, a haloaryl group, an arylsulfonyl-lower alkyl group, an arylsulfonylamino group, an aryl-lower alkyloxy group, an aryl-lower alkyl group, a quinolyl group, an isoquinolyl group, an aryloxy group, an arylcarbonyl group, an arylcarbonylamino group, and an aryl-lower alkyloxy group substituted by one or two halogen atoms;

R_{28} represents a hydrogen atom, an alkyl group having up to 7 carbon atoms, a halo-lower alkyl group, a lower alkoxy-lower alkyl group, a lower cycloalkyl group, an aryl group, an aryl-lower alkyl group, a lower alkylamino group, a lower alkoxy group, a lower alkylthio group, a hydroxyl group, a mercapto group, an amino group, or a carboxyl group;

R_{25} represents an alkyl group having up to 8 carbon atoms, a halo-lower alkyl group, a tri-lower alkylsilyl-lower alkyl group, a lower alkoxy-lower alkyl group, a lower alkylthio-lower alkyl group, an aryl group, a quinolyl group, an isoquinolyl group, an aryl-lower alkyl group, or a hydroxy-lower alkyl group; said aryl group may be substituted by a halogen atom, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, or a nitro group;

R_{26} represents a hydrogen atom or a lower alkyl group; provided that, when R_{25} and R_{26} are both lower alkyl groups, they may be bonded together to form a ring;

Y represents a carbonyl group or a lower alkylene group;

A represents a single bond, or a lower alkylene or alkenylene group; and

R_{29} represents a hydrogen atom or a lower alkyl group.

2. The benzimidazole derivative or its pharmaceutically acceptable salt of claim 1, wherein R_{27} represents an aryl-lower alkyl group whole aromatic ring moiety may be substituted by one or two substituents selected from the group consisting of the group consisting of a halogen atom, a lower alkyl group, a halo-lower alkyl group, a cyanoaryl group, an amino group, a lower alkoxy group, a nitro group, a cyano group, an aryl group, a haloaryl group, an arylsulfonyl-lower alkyl group, an arylsulfonylamino group, an aryl-lower alkyloxy group, an aryl-lower alkyl group, a quinolyl group, an isoquinolyl group, an arylcarbonylamino group, and an aryl-lower alkyloxy group substituted by one or two halogen atoms;

R_{25} represents an alkyl group having up to 8 carbon atoms, a halo-lower alkyl group, a tri-lower alkylsilyl-lower alkyl group, a lower alkoxy-lower alkyl group, a lower alkylthio-lower alkyl group, an aryl group, a quinolyl group, an isoquinolyl group, an aryloxy group, an arylcarbonyl group, an aryl-lower alkyl group, or a hydroxy-lower alkyl group; said aryl group may be substituted by a halogen atom, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, or a nitro group;

Y represents a carbonyl group; and

A represents a single bond.

3. The benzimidazole derivative or its pharmaceutically acceptable salt of claim 1, wherein R_{27} represents an aryl-lower alkyl group whose aromatic ring moiety may be substituted by one or two substituents selected from the group consisting of a halogen atom and an aryl group;

R_{28} represents an alkyl group having up to 7 carbon atoms or a lower cycloalkyl group;

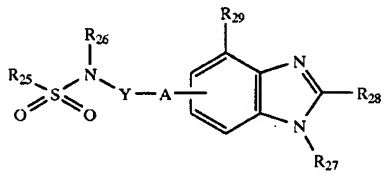
Y represents a carbonyl group; and

A represents a single bond.

4. The benzimidazole derivative or its pharmaceutically acceptable salt of claim 1, wherein said derivative is selected from the group consisting of 6-benzenesulfonylcarbamoyl-1-(2-chlorobenzyl)-2-methylbenzimidazole, 1-(biphenyl-4-ylmethyl)-6-(1-butanesulfonylcarbamoyl)-2-methylbenzimidazole, 1-(biphenyl-4-ylmethyl)-6-(1-butanesulfonylcarbamoyl)-2-ethylbenzimidazole, 6-benzenesulfonylcarbamoyl-2-cyclopropyl-1-(2-fluorobenzyl)benzimidazole, 6-benzenesulfonylcarbamoyl-1-(2,4-dichlorobenzyl)- 2-methylbenzimidazole, 6-benzenesulfonylcarbamoyl-1-(2,4-difluorobenzyl-2-methylbenzimidazole, 6-(1-butanesulfonylcarbamoyl)-1-[(3-fluorobiphenyl-4-yl)methyl]-2-methylbenzimidazole, 1-(2,4-dichlorobenzyl)-2-methyl-6-(1-pentanesulfonylcarbamoyl)benzimidazole, and 1-(4-biphenylmethyl)-2-ethyl-6-(1-pentanesulfonylcarbamoyl) benzimidazole.

5. A pharmaceutical composition comprising a compound of formula (IX) or its pharmaceutically acceptable salt:

(IX)



wherein R_{27} represents a hydrogen atom, an alkyl group having up to 7 carbon atoms, a halo-lower alkyl group, an arylsulfonyl group, an aryl-lower alkyl group, a quinolyl-lower alkyl group, an isoquinolyl-lower alkyl group, a halo-quinolyl-lower alkyl group, or a halo-isoquinolyl-lower alkyl group; the aromatic ring moiety in said aryl-lower alkyl group may be substituted by one or two substituents selected from the group consisting of a halogen atom, a lower alkyl group, a halo-lower alkyl group, a cyanoaryl group, an amino group, a lower alkoxy group, a nitro group, a cyano group, an aryl group, a haloaryl group, an arylsulfonyl-lower alkyl group, an arylsulfonylamino group, an aryl-lower alkyloxy group, an aryl-lower alkyl group, a quinolyl group, an isoquinolyl group, an aryloxy group, an arylcarbonyl group, an arylcarbonylamino group, and an aryl-lower alkyloxy group substituted by one or two halogen atoms;

R_{28} represents a hydrogen atom, an alkyl group having up to 7 carbon atoms, a halo-lower alkyl group, a lower alkoxy-lower alkyl group, a lower cycloalkyl group, an aryl group, an aryl-lower alkyl group, a lower alkylamino group, a lower alkoxy group, a lower alkylthio group, a hydroxyl group, a mercapto group, an amino group, or a carboxyl group;

R_{25} represents an alkyl group having up to 8 carbon atoms, a halo-lower alkyl group, a tri-lower alkylsilyl-lower alkyl group, a lower alkoxy-lower alkyl group, a lower alkylthio-lower alkyl group, an aryl group, a quinolyl group, an isoquinolyl group, an aryl-lower alkyl group, or a hydroxy-lower alkyl group; said aryl group may be substituted by a halogen atom, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, or a nitro group;

R_{26} represents a hydrogen atom or a lower alkyl group; provided that, when R_{25} and R_{26} are both lower alkyl groups, they may be bonded together to form a ring;

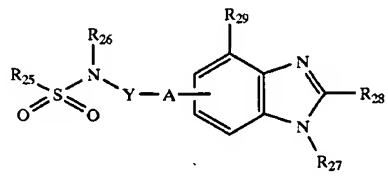
Y represents a carbonyl group or a lower alkylene group;

A represents a single bond, or a lower alkylene or alkenylene group; and

R_{29} represents a hydrogen atom or a lower alkyl group, and a pharmaceutically acceptable excipient.

6. A method for lowering the blood sugar of a patient and/or inhibiting PDE5 in a patient, which comprises administering to the patient an effective amount of a compound of formula (IX) or its pharmaceutically acceptable salt:

(IX)



wherein R_{27} represents a hydrogen atom, an alkyl group having up to 7 carbon atoms, a halo-lower alkyl group, an arylsulfonyl group, an aryl-lower alkyl group, a quinolyl-lower alkyl group, an isoquinolyl-lower alkyl group, a halo-quinolyl-lower alkyl group, or a halo-isoquinolyl-lower alkyl group; the aromatic ring moiety in said aryl-lower alkyl group may be substituted by one or two substituents selected from the group consisting of a halogen atom, a lower alkyl group, a halo-lower alkyl group, a cyanoaryl group, an amino group, a lower alkoxy group, a nitro group, a cyano group, an aryl group, a haloaryl group, an arylsulfonyl-lower alkyl group, an arylsulfonylamino group, an aryl-lower alkyloxy group, an aryl-lower alkyl group, a quinolyl group, an isoquinolyl group, an aryloxy group, an arylcarbonyl group, an arylcarbonylamino group, and an aryl-lower alkyloxy group substituted by one or two halogen atoms;

R_{28} represents a hydrogen atom, an alkyl group having up to 7 carbon atoms, a halo-lower alkyl group, a lower alkoxy-lower alkyl group, a lower cycloalkyl group, an aryl group, an aryl-lower alkyl group, a lower alkylamino group, a lower alkoxy group, a lower alkylthio group, a hydroxyl group, a mercapto group, an amino group, or a carboxyl group;

R_{25} represents an alkyl group having up to 8 carbon atoms, a halo-lower alkyl group, a tri-lower alkylsilyl-lower alkyl group, a lower alkoxy-lower alkyl group, a lower alkylthio-lower alkyl group, an aryl group, a quinolyl group, an isoquinolyl group, an aryl-lower alkyl group, or a hydroxy-lower alkyl group; said aryl group may be substituted by a halogen atom, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, or a nitro group;

R_{26} represents a hydrogen atom or a lower alkyl group; provided that, when R_{25} and R_{26} are both lower alkyl groups, they may be bonded together to form a ring;

Y represents a carbonyl group or a lower alkylene group;

A represents a single bond, or a lower alkylene or alkenylene group; and

R_{29} represents a hydrogen atom or a lower alkyl group.

* * * * *

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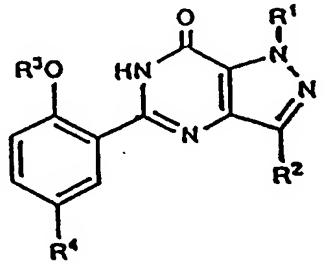
(54) Title: PYRAZOLOPYRIMIDINONES FOR THE TREATMENT OF IMPOTENCE

(57) Abstract

The use of a compound of formula (I) wherein R^1 is H; C_1-C_3 alkyl; C_1-C_3 perfluoroalkyl; or C_3-C_5 cycloalkyl; R^2 is H; optionally substituted C_1-C_6 alkyl; C_1-C_3 perfluoroalkyl; or C_3-C_6 cycloalkyl; R^3 is optionally substituted C_1-C_6 alkyl; C_1-C_6 perfluoroalkyl; C_3-C_5 cycloalkyl; C_3-C_6 alkenyl; or C_3-C_6 alkynyl; R^4 is optionally substituted C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkanoyl, (hydroxy)C_2-C_4 alkyl or (C_2-C_3 alkoxy)C_1-C_2 alkyl; $CONR^5R^6$; CO_2R^7; halo; NR^5R^6; $NHSO_2NR^5R^6$; $NHSO_2R^8$; $SO_2NR^9R^{10}$; or phenyl, pyridyl, pyrimidinyl, imidazolyl, oxazolyl, thiazolyl, thienyl or triazolyl any of which is optionally substituted with methyl; R^5 and R^6 are each independently H or C_1-C_4 alkyl, or together with the nitrogen atom to which they are attached form an optionally substituted pyrrolidinyl, piperidino, morpholino, 4-N(R^{11})-piperazinyl or imidazolyl group; R^7 is H or C_1-C_4 alkyl; R^8 is optionally substituted C_1-C_3 alkyl; R^9 and R^{10} together with the nitrogen atom to which they are attached form an optionally substituted pyrrolidinyl, piperidino, morpholino or 4-N(R^{12})-piperazinyl group; R^{11} is H; optionally substituted C_1-C_3 alkyl; (hydroxy)C_2-C_3 alkyl; or C_1-C_4 alkanoyl; R^{12} is H; optionally substituted C_1-C_6 alkyl; $CONR^{13}R^{14}$; $CSNR^{13}R^{14}$; or $C(NH)NR^{13}R^{14}$; and R?13? and R^{14} are each independently H; C_1-C_4 alkyl; or substituted C_2-C_4 alkyl; or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing either entity, for the manufacture of a medicament for the curative or prophylactic treatment of erectile dysfunction in a male animal, including man; a pharmaceutical composition for said treatment; and a method of said treatment of said male animal with said pharmaceutical composition or with said either entity.



(I)

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PYRAZOLOPYRIMIDINONES FOR THE TREATMENT OF IMPOTENCE

This invention relates to the use of a series of pyrazolo[4,3-d]pyrimidin-7-ones for the treatment of impotence.

Impotence can be defined literally as a lack of power, in the male, to copulate and may involve an inability to achieve penile erection or ejaculation, or both. More specifically, erectile impotence or dysfunction may be defined as an inability to obtain or sustain an erection adequate for intercourse. Its prevalence is claimed to be between 2 and 7% of the human male population, increasing with age, up to 50 years, and between 18 and 75% between 55 and 80 years of age. In the USA alone, for example, it has been estimated that there are up to 10 million impotent males, with the majority suffering from problems of organic rather than of psychogenic origin.

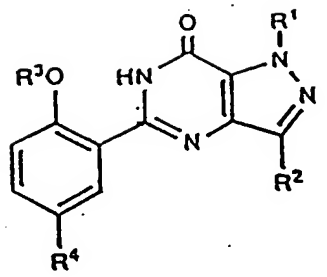
Reports of well-controlled clinical trials in man are few and the efficacy of orally administered drugs is low. Although many different drugs have been shown to induce penile erection, they are only effective after direct injection into the penis, e.g. intraurethrally or intracavernosally (i.c.), and are not approved for erectile dysfunction. Current medical treatment is based on the i.c injection of vasoactive substances and good results have been claimed with phenoxybenzamine, phentolamine, papaverine and prostaglandin E_1, either alone or in combination; however, pain, priapism and fibrosis of the penis are associated with the i.c. administration of some of these agents. Potassium channel openers (KCO) and vasoactive intestinal polypeptide (VIP) have also been shown to be active i.c., but cost and stability issues could limit development of the latter. An alternative to the i.c. route is the use of glyceryl trinitrate (GTN) patches applied to the penis, which has been

shown to be effective but produces side-effects in both patient and partner.

As a general alternative to pharmacological intervention, a variety of penile prostheses has been used to assist achievement of an erection. The short term success rate is good, but problems with infection and ischaemia, especially in diabetic men, make this type of treatment a final option rather than first-line therapy.

The compounds of the invention are potent inhibitors of cyclic guanosine 3',5'-monophosphate phosphodiesterases (cGMP PDEs) in contrast to their inhibition of cyclic adenosine 3',5'-monophosphate phosphodiesterases (cAMP PDEs). This selective enzyme inhibition leads to elevated cGMP levels which, in turn, provides the basis for the utilities already disclosed for the said compounds in EP-A-0463756 and EP-A-0526004, namely in the treatment of stable, unstable and variant (Prinzmetal) angina, hypertension, pulmonary hypertension, congestive heart failure, atherosclerosis, conditions of reduced blood vessel patency e.g. post-percutaneous transluminal coronary angioplasty (post-PTCA), peripheral vascular disease, stroke, bronchitis, allergic asthma, chronic asthma, allergic rhinitis, glaucoma, and diseases characterised by disorders of gut motility, e.g. irritable bowel syndrome (IBS).

Unexpectedly, it has now been found that these disclosed compounds are useful in the treatment of erectile dysfunction. Furthermore the compounds may be administered orally, thereby obviating the disadvantages associated with i.c. administration. Thus the present invention concerns the use of a compound of formula (I):



(I)

wherein R^1 is H; C_1-C_3 alkyl; C_1-C_3 perfluoroalkyl; or C_3-C_5 cycloalkyl;
R^2 is H; C_1-C_6 alkyl optionally substituted with C_3-C_6 cycloalkyl; C_1-C_3 perfluoroalkyl; or C_3-C_6 cycloalkyl;
R^3 is C_1-C_6 alkyl optionally substituted with C_3-C_6 cycloalkyl; C_1-C_6 perfluoroalkyl; C_3-C_5 cycloalkyl; C_3-C_6 alkenyl; or C_3-C_6 alkynyl;
R^4 is C_1-C_4 alkyl optionally substituted with OH, NR^5R^6, CN, $CONR^5R^6$ or CO_2R^7; C_2-C_4 alkenyl optionally substituted with CN, $CONR^5R^6$ or CO_2R^7; C_2-C_4 alkanoyl optionally substituted with NR^5R^6; (hydroxy)C_2-C_4 alkyl optionally substituted with NR^5R^6; (C_2-C_3 alkoxy)C_1-C_2 alkyl optionally substituted with OH or NR^5R^6; $CONR^5R^6$; CO_2R^7; halo; NR^5R^6; $NHSO_2NR^5R^6$; $NHSO_2R^8$; $SO_2NR^9R^{10}$; or phenyl, pyridyl, pyrimidinyl, imidazolyl, oxazolyl, thiazolyl, thienyl or triazolyl any of which is optionally substituted with methyl;
R^5 and R^6 are each independently H or C_1-C_4 alkyl, or together with the nitrogen atom to which they are attached form a pyrrolidinyl, piperidino, morpholino, 4-N(R^{11})-piperazinyl or imidazolyl group wherein said group is optionally substituted with methyl or OH;

R^7 is H or C_1-C_4 alkyl;

R^8 is C_1-C_3 alkyl optionally substituted with NR^5R^6;

R^9 and R^{10} together with the nitrogen atom to which they are attached form a pyrrolidinyl, piperidino, morpholino or 4-N(R^{12})-piperazinyl group wherein said group is optionally substituted with C_1-C_4 alkyl, C_1-C_3 alkoxy, $NR^{13}R^{14}$ or $CONR^{13}R^{14}$;

R^{11} is H; C_1-C_3 alkyl optionally substituted with phenyl; (hydroxy)C_2-C_3 alkyl; or C_1-C_4 alkanoyl;

R^{12} is H; C_1-C_6 alkyl; (C_1-C_3 alkoxy)C_2-C_6 alkyl; (hydroxy)C_2-C_6 alkyl; ($R^{13}R^{14}N$)C_2-C_6 alkyl; ($R^{13}R^{14}NOC$)C_1-C_6 alkyl; $CONR^{13}R^{14}$; $CSNR^{13}R^{14}$; or $C(NH)NR^{13}R^{14}$;

and R^{13} and R^{14} are each independently H; C_1-C_4 alkyl; (C_1-C_3 alkoxy)C_2-C_4 alkyl; or (hydroxy)C_2-C_4 alkyl;

or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing either entity, for the manufacture of a medicament for the curative or prophylactic treatment of erectile dysfunction in a male animal, including man.

In the above definition, unless otherwise indicated, alkyl groups having three or more carbon atoms, alkenyl and alkynyl groups having four or more carbon atoms, alkoxy groups having three carbon atoms and alkanoyl groups having four carbon atoms may be straight chain or branched chain. Halo means fluoro, chloro, bromo or iodo.

The compounds of formula (I) may contain one or more asymmetric centres and thus they can exist as enantiomers or diastereoisomers. Furthermore, certain compounds of formula (I) which contain alkenyl groups

may exist as cis-isomers or trans-isomers. In each instance, the invention includes both mixtures and separate individual isomers.

The compounds of formula (I) may also exist in tautomeric forms and the invention includes both mixtures and separate individual tautomers.

The pharmaceutically acceptable salts of the compounds of formula (I) which contain a basic centre are, for example, non-toxic acid addition salts formed with inorganic acids such as hydrochloric, hydrobromic, sulphuric and phosphoric acid, with organo-carboxylic acids, or with organo-sulphonic acids. Compounds of formula (I) can also provide pharmaceutically acceptable metal salts, in particular non-toxic alkali metal salts, with bases. Examples include the sodium and potassium salts.

A preferred group of compounds of formula (I) is that wherein R^1 is H, methyl or ethyl; R^2 is C_1-C_3 alkyl; R^3 is C_2-C_3 alkyl or allyl; R^4 is C_1-C_2 alkyl optionally substituted with OH, NR^5R^6, CN, $CONR^5R^6$ or CO_2R^7; acetyl optionally substituted with NR^5R^6; hydroxyethyl optionally substituted with NR^5R^6; ethoxymethyl optionally substituted with OH or NR^5R^6; CH=CHCN; $CH=CHCONR^5R^6$; $CH=CHCO_2R^7$; $CONR^5R^6$; CO_2H; Br; NR^5R^6; $NHSO_2NR^5R^6$; $NHSO_2R^8$; $SO_2NR^9R^{10}$; or pyridyl or imidazolyl either of which is optionally substituted with methyl; R^5 and R^6 are each independently H, methyl or ethyl, or together with the nitrogen atom to which they are attached form a piperidino, morpholino, 4-$N(R^{11})$-piperazinyl or imidazolyl group wherein said group is optionally substituted with methyl or OH; R^7 is H or t-butyl; R^8 is methyl or $CH_2CH_2CH_2NR^5R^6$; R^9 and R^{10} together with the nitrogen atom to which they are attached form a piperidino or 4-$N(R^{12})$-piperazinyl group wherein said group is optionally substituted with $NR^{13}R^{14}$ or $CONR^{13}R^{14}$; R^{11} is H, methyl, benzyl, 2-

hydroxyethyl or acetyl; R^{12} is H, C_1-C_3 alkyl, (hydroxy)C_2-C_3 alkyl, $CSNR^{13}R^{14}$ or $C(NH)NR^{13}R^{14}$; and R^{13} and R^{14} are each independently H or methyl.

A more preferred group of compounds of formula (I) is that wherein R^1 is methyl or ethyl; R^2 is C_1-C_3 alkyl; R^3 is ethyl, n-propyl or allyl; R^4 is $CH_2NR^5R^6$, $COCH_2NR^5R^6$, $CH(OH)CH_2NR^5R^6$, $CH_2OCH_2CH_3$, $CH_2OCH_2CH_2OH$, $CH_2OCH_2CH_2NR^5R^6$, $CH=CHCON(CH_3)_2$, $CH=CHCO_2R^7$, $CONR^5R^6$, CO_2H, Br, $NHSO_2NR^5R^6$, $NHSO_2CH_2CH_2CH_2NR^5R^6$, $SO_2NR^9R^{10}$, 2-pyridyl, 1-imidazolyl or 1-methyl-2-imidazolyl; R^5 and R^6 together with the nitrogen atom to which they are attached form a piperidino, 4-hydroxypiperidino, morpholino, 4-$N(R^{11})$-piperazinyl or 2-methyl-1-imidazolyl group; R^7 is H or t-butyl; R^9 and R^{10} together with the nitrogen atom to which they are attached form a 4-carbamoylpiperidino or 4-$N(R^{12})$-piperazinyl group; R^{11} is H, methyl, benzyl, 2-hydroxyethyl or acetyl; and R^{12} is H, C_1-C_3 alkyl, 2-hydroxyethyl or $CSNH_2$.

A particularly preferred group of compounds of formula (I) is that wherein R^1 is methyl or ethyl; R^2 is n-propyl; R^3 is ethyl, n-propyl or allyl; R^4 is $COCH_2NR^5R^6$, $CONR^5R^6$, $SO_2NR^9R^{10}$ or 1-methyl-2-imidazolyl; R^5 and R^6 together with the nitrogen atom to which they are attached form a morpholino or 4-$N(R^{11})$-piperazinyl group; R^9 and R^{10} together with the nitrogen atom to which they are attached form a 4-$N(R^{12})$-piperazinyl group; R^{11} is methyl or acetyl; and R^{12} is H, methyl, 2-propyl or 2-hydroxyethyl.

Especially preferred individual compounds of the invention include:

5-(2-ethoxy-5-morpholinoacetylphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

5-(5-morpholinoacetyl-2-n-propoxyphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

5-[2-ethoxy-5-(4-methyl-1-piperazinylsulphonyl)-phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

5-[2-allyloxy-5-(4-methyl-1-piperazinylsulphonyl)-phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

5-{2-ethoxy-5-[4-(2-propyl)-1-piperazinyl-sulphonyl]phenyl}-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

5-{2-ethoxy-5-[4-(2-hydroxyethyl)-1-piperazinyl-sulphonyl]phenyl}-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

5-{5-[4-(2-hydroxyethyl)-1-piperazinylsulphonyl]-2-n-propoxyphenyl}-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

5-[2-ethoxy-5-(4-methyl-1-piperazinylcarbonyl)-phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

and 5-[2-ethoxy-5-(1-methyl-2-imidazolyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one.

The compounds of formula (I) and their pharmaceutically acceptable salts, processes for the preparation thereof, in vitro test methods for determining the cGMP PDE and cAMP PDE inhibitory activities thereof, pharmaceutical compositions thereof and routes of administration for human use, are described in EP-A-0463756 and EP-A-0526004.

A preliminary investigation was carried out with a view to isolating and characterising the cyclic nucleotide PDEs of human corpus cavernosum, relaxation of which leads to penile erection. Studies of substrate specificity, response to activators and inhibitor sensitivity, have demonstrated that human corpus cavernosum contains three distinct PDE enzymes.

Methods

Fresh frozen human penis was obtained from IIAM (Pennsylvania). Tissue was thawed at room temperature, the corpus cavernosum was dissected from the penis to yield approximately 2-4 g of tissue and the following isolation protocol was followed. Tissue was coarsely chopped in ice-cold isotonic buffer (35 ml) containing 250mM sucrose, 1mM EDTA, 0.5mM PMSF and 20mM HEPES, pH 7.2, and the mixture subjected to brief (1 min.) treatment with a Silversen mixer/emulsifier. Homogenates were prepared using homogeniser tubes with teflon pestles and soluble fraction was prepared by centrifugation at 100,000 x g for 60 min. at 4°C. 10 ml of high speed supernatant was applied to a Pharmacia Mono Q anion exchange column (1 ml bed volume) equilibrated with buffer containing 1mM EDTA, 0.5 mM PMSF and 20mM HEPES, pH 7.2 (chromatography buffer). The column was then washed with 5 bed volumes of chromatography buffer, after which PDEs were eluted using a continuous gradient of 0-500mM NaCl (total volume 35 ml) and 1 ml fractions collected.

Column fractions were assayed for PDE activity using 500nM cGMP or 500nM cAMP as substrate. cAMP PDE activity was also determined in the presence of 1μM unlabelled cGMP and the PDE activity of selected fractions was determined in the presence of 10mM $CaCl_2$ and 10 units/ml bovine brain calmodulin. Appropriate fractions were pooled and stored at 4°C during the course of the study.

Inhibition studies were performed using a substrate concentration of 500nM throughout. All inhibitors were dissolved in DMSO and concentration-response curves were constructed over the range 3 x 10^{-10} to 1 x 10^{-4}M in half log increments. IC_{50} values were calculated using the sigmoidal curve fitting algorithm of biostat.

Results

Human corpus cavernosum soluble PDEs were separated into three distinct fractions of activity. The first, fraction I, (designated by order of elution) represents the major PDE present and is highly selective for cGMP as substrate. This fraction was found to be insensitive to stimulation by calcium/calmodulin and was classified as PDE_V. Fraction II hydrolyses cGMP and cAMP, with the latter activity being stimulated in the presence of cGMP, and is classified as PDE_{II}, whilst fraction III is cAMP selective and this activity is inhibited in the presence of cGMP, consistent with PDE_{III} activity.

In order to further characterise the PDE isoenzymes present in the tissue, studies were performed using a variety of inhibitors. Inhibitor studies with fractions I and II were performed using cGMP as substrate, whilst fraction III studies utilised cAMP. These studies confirmed that fraction I corresponds to PDE_V, whilst fraction III was clearly identified as PDE_{III}; fraction II (PDE_{II}) was relatively insensitive to all the inhibitors tested.

In summary, the above investigation identified three PDE isoenzymes in human corpus cavernosum tissue. The predominant PDE is the cGMP-specific PDE_V, whilst cGMP-stimulated cAMP PDE_{II} and cGMP-inhibited cAMP PDE_{III} are also present.

The compounds of the invention have been tested in vitro and found to be potent and selective inhibitors of the cGMP-specific PDE_V. For example, one of the especially preferred compounds of the invention has an IC_{50} = 6.8 nM v. the PDE_V enzyme, but demonstrates only weak inhibitory activity against the PDE_{II} and PDE_{III} enzymes with IC_{50} = >100 μM and 34 μM respectively. Thus relaxation of the corpus cavernosum tissue and

consequent penile erection is presumably mediated by elevation of cGMP levels in the said tissue, by virtue of the PDE inhibitory profile of the compounds of the invention.

Furthermore, none of the compounds of the invention tested in rat and dog, both intravenously (i.v.) and orally (p.o.) at up to 3 mg/Kg, has shown any overt sign of adverse acute toxicity. In mouse, no deaths occurred after doses of up to 100 mg/Kg i.v.. Certain especially preferred compounds showed no toxic effects on chronic p.o. administration to rat at up to 10 mg/Kg and to dog at up to 20 mg/Kg.

In man, certain especially preferred compounds have been tested orally in both single dose and multiple dose volunteer studies. Moreover, patient studies conducted thus far have confirmed that one of the especially preferred compounds induces penile erection in impotent males.

Although the compounds of the invention are envisaged primarily for the treatment of erectile dysfunction or male sexual dysfunction, they may also be useful for the treatment of female sexual dysfunction including orgasmic dysfunction related to clitoral disturbances.

Generally, in man, oral administration of the compounds of the invention is the preferred route, being the most convenient and avoiding the disadvantages associated with i.c. administration. A preferred dosing regimen for a typical man is 5 to 75 mg of compound three times daily. In circumstances where the recipient suffers from a swallowing disorder or from impairment of drug absorption after oral administration, the drug may be administered parenterally, e.g. sublingually or buccally.

For veterinary use, a compound of formula (I) or a non-toxic salt thereof is administered as a suitably acceptable formulation in accordance with

normal veterinary practice and the veterinary surgeon will determine the dosing regimen and route of administration which will be most appropriate for a particular male animal.

Thus the invention includes a pharmaceutical composition for the curative or prophylactic treatment of erectile dysfunction in a male animal, including man, comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable diluent or carrier.

There is further provided a process for the preparation of a pharmaceutical composition for the curative or prophylactic treatment of erectile dysfunction in a male animal, including man, comprising formulating a compound of formula (I), or a pharmaceutically acceptable salt thereof, with a pharmaceutically acceptable diluent or carrier.

The invention also provides a method of treating a male animal, including man, to cure or prevent erectile dysfunction which comprises treating said male animal with an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing either entity.

In a further aspect, the invention includes the use of a cGMP PDE inhibitor, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing either entity, for the treatment of erectile dysfunction in a male animal, including man.

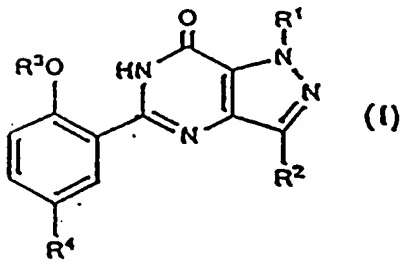
The invention also includes a method of treating a male animal, including man, to cure or prevent erectile dysfunction, which comprises treating said male animal with an effective amount of a cGMP PDE inhibitor, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing either entity.

Moreover, the invention includes the use of a cGMP PDE inhibitor, or a pharmaceutically acceptable salt

thereof, or a pharmaceutical composition containing either entity, for the manufacture of a medicament for the curative or prophylactic treatment of erectile dysfunction in a male animal, including man.

CLAIMS

1. The use of a compound of formula (I):



(I)

wherein R^1 is H; C_1-C_3 alkyl; C_1-C_3 perfluoroalkyl; or C_3-C_5 cycloalkyl;
R^2 is H; C_1-C_6 alkyl optionally substituted with C_3-C_6 cycloalkyl; C_1-C_3 perfluoroalkyl; or C_3-C_6 cycloalkyl;
R^3 is C_1-C_6 alkyl optionally substituted with C_3-C_6 cycloalkyl; C_1-C_6 perfluoroalkyl; C_3-C_5 cycloalkyl; C_3-C_6 alkenyl; or C_3-C_6 alkynyl;
R^4 is C_1-C_4 alkyl optionally substituted with OH, NR^5R^6, CN, $CONR^5R^6$ or CO_2R^7; C_2-C_4 alkenyl optionally substituted with CN, $CONR^5R^6$ or CO_2R^7; C_2-C_4 alkanoyl optionally substituted with NR^5R^6; (hydroxy)C_2-C_4 alkyl optionally substituted with NR^5R^6; (C_2-C_3 alkoxy)C_1-C_2 alkyl optionally substituted with OH or NR^5R^6; $CONR^5R^6$; CO_2R^7; halo; NR^5R^6; $NHSO_2NR^5R^6$; $NHSO_2R^8$; $SO_2NR^9R^{10}$; or phenyl, pyridyl, pyrimidinyl, imidazolyl, oxazolyl, thiazolyl, thienyl or triazolyl any of which is optionally substituted with methyl;
R^5 and R^6 are each independently H or C_1-C_4 alkyl, or together with the nitrogen atom to which they are attached form a pyrrolidinyl, piperidino, morpholino, 4-N(R^{11})-piperazinyl

or imidazolyl group wherein said group is optionally substituted with methyl or OH;

R^7 is H or C_1-C_4 alkyl;

R^8 is C_1-C_3 alkyl optionally substituted with NR^5R^6;

R^9 and R^{10} together with the nitrogen atom to which they are attached form a pyrrolidinyl, piperidino, morpholino or 4-$N(R^{12})$-piperazinyl group wherein said group is optionally substituted with C_1-C_4 alkyl, C_1-C_3 alkoxy, $NR^{13}R^{14}$ or $CONR^{13}R^{14}$;

R^{11} is H; C_1-C_3 alkyl optionally substituted with phenyl; (hydroxy)C_2-C_3 alkyl; or C_1-C_4 alkanoyl;

R^{12} is H; C_1-C_6 alkyl; (C_1-C_3 alkoxy)C_2-C_6 alkyl; (hydroxy)C_2-C_6 alkyl; ($R^{13}R^{14}N$)C_2-C_6 alkyl; ($R^{13}R^{14}NOC$)C_1-C_6 alkyl; $CONR^{13}R^{14}$; $CSNR^{13}R^{14}$; or $C(NH)NR^{13}R^{14}$;

and R^{13} and R^{14} are each independently H; C_1-C_4 alkyl; (C_1-C_3 alkoxy)C_2-C_4 alkyl; or (hydroxy)C_2-C_4 alkyl;

or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing either entity, for the manufacture of a medicament for the curative or prophylactic treatment of erectile dysfunction in a male animal, including man.

2. The use according to claim 1 wherein in the compound of formula (I) R^1 is H, methyl or ethyl; R^2 is C_1-C_3 alkyl; R^3 is C_2-C_3 alkyl or allyl; R^4 is C_1-C_2 alkyl optionally substituted with OH, NR^5R^6, CN, $CONR^5R^6$ or CO_2R^7; acetyl optionally substituted with NR^5R^6; hydroxyethyl optionally substituted with NR^5R^6; ethoxymethyl optionally substituted with OH or NR^5R^6; CH=CHCN; $CH=CHCONR^5R^6$; $CH=CHCO_2R^7$; $CONR^5R^6$; CO_2H; Br; NR^5R^6; $NHSO_2NR^5R^6$; $NHSO_2R^8$; $SO_2NR^9R^{10}$; or pyridyl or

imidazolyl either of which is optionally substituted with methyl; R^5 and R^6 are each independently H, methyl or ethyl, or together with the nitrogen atom to which they are attached form a piperidino, morpholino, 4-$N(R^{11})$-piperazinyl or imidazolyl group wherein said group is optionally substituted with methyl or OH; R^7 is H or t-butyl; R^8 is methyl or $CH_2CH_2CH_2NR^5R^6$; R^9 and R^{10} together with the nitrogen atom to which they are attached form a piperidino or 4-$N(R^{12})$-piperazinyl group wherein said group is optionally substituted with $NR^{13}R^{14}$ or $CONR^{13}R^{14}$; R^{11} is H, methyl, benzyl, 2-hydroxyethyl or acetyl; R^{12} is H, C_1-C_3 alkyl, (hydroxy)C_2-C_3 alkyl, $CSNR^{13}R^{14}$ or $C(NH)NR^{13}R^{14}$; and R^{13} and R^{14} are each independently H or methyl.

3. The use according to claim 2 wherein in the compound of formula (I) R^1 is methyl or ethyl; R^2 is C_1-C_3 alkyl; R^3 is ethyl, n-propyl or allyl; R^4 is $CH_2NR^5R^6$, $COCH_2NR^5R^6$, $CH(OH)CH_2NR^5R^6$, $CH_2OCH_2CH_3$, $CH_2OCH_2CH_2OH$, $CH_2OCH_2CH_2NR^5R^6$, $CH{=}CHCON(CH_3)_2$, $CH{=}CHCO_2R^7$, $CONR^5R^6$, CO_2H, Br, $NHSO_2NR^5R^6$, $NHSO_2CH_2CH_2CH_2NR^5R^6$, $SO_2NR^9R^{10}$, 2-pyridyl, 1-imidazolyl or 1-methyl-2-imidazolyl; R^5 and R^6 together with the nitrogen atom to which they are attached form a piperidino, 4-hydroxypiperidino, morpholino, 4-$N(R^{11})$-piperazinyl or 2-methyl-1-imidazolyl group; R^7 is H or t-butyl; R^9 and R^{10} together with the nitrogen atom to which they are attached form a 4-carbamoylpiperidino or 4-$N(R^{12})$-piperazinyl group; R^{11} is H, methyl, benzyl, 2-hydroxyethyl or acetyl; and R^{12} is H, C_1-C_3 alkyl, 2-hydroxyethyl or $CSNH_2$.

4. The use according to claim 3 wherein in the compound of formula (I) R^1 is methyl or ethyl; R^2 is n-propyl; R^3 is ethyl, n-propyl or allyl; R^4 is $COCH_2NR^5R^6$, $CONR^5R^6$, $SO_2NR^9R^{10}$ or 1-methyl-2-imidazolyl; R^5 and R^6 together with the nitrogen atom to which they are attached form a morpholino or 4-$N(R^{11})$-piperazinyl

group; R^9 and R^{10} together with the nitrogen atom to which they are attached form a 4-N(R^{12})-piperazinyl group; R^{11} is methyl or acetyl; and R^{12} is H, methyl, 2-propyl or 2-hydroxyethyl.

5. The use according to claim 4 wherein the compound of formula (I) is selected from:

5-(2-ethoxy-5-morpholinoacetylphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

5-(5-morpholinoacetyl-2-n-propoxyphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

5-[2-ethoxy-5-(4-methyl-1-piperazinylsulphonyl)-phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

5-[2-allyloxy-5-(4-methyl-1-piperazinylsulphonyl)-phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

5-{2-ethoxy-5-[4-(2-propyl)-1-piperazinyl-sulphonyl]phenyl}-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

5-{2-ethoxy-5-[4-(2-hydroxyethyl)-1-piperazinyl-sulphonyl]phenyl}-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

5-{5-[4-(2-hydroxyethyl)-1-piperazinylsulphonyl]-2-n-propoxyphenyl}-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

5-[2-ethoxy-5-(4-methyl-1-piperazinylcarbonyl)-phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

and 5-[2-ethoxy-5-(1-methyl-2-imidazolyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one.

6. A pharmaceutical composition for the curative or prophylactic treatment of erectile dysfunction in a male animal, including man, comprising a compound of formula (I) according to any one of claims 1 to 5, or a pharmaceutically acceptable salt thereof, together

with a pharmaceutically acceptable diluent or carrier.

7. A process for the preparation of a pharmaceutial composition for the curative or prophylactic treatment of erectile dysfunction in a male animal, including man, comprising formulating a compound of formula (I) according to any one of claims 1 to 5, or a pharmaceutically acceptable salt thereof, with a pharmaceutically acceptable diluent or carrier.

8. A method of treating a male animal, including man, to cure or prevent erectile dysfunction which comprises treating said male animal with an effective amount of a compound of formula (I) according to any one of claims 1 to 5, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing either entity.

9. The use of a cGMP PDE inhibitor, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing either entity, for the treatment of erectile dysfunction in a male animal, including man.

10. A method of treating a male animal, including man, to cure or prevent erectile dysfunction, which comprises treating said male animal with an effective amount of a cGMP PDE inhibitor, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing either entity.

11. The use of a cGMP PDE inhibitor, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing either entity, for the manufacture of a medicament for the curative or prophylactic treatment of erectile dysfunction in a male animal, including man.

INTERNATIONAL SEARCH REPORT

Inte nal Application No
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 A61K31/505

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 463 756 (PFIZER INC.) 2 January 1992 cited in the application see claims 1-9	6,7
X	EP,A,0 526 004 (PFIZER INC.) 3 February 1993 cited in the application see claims 1-8	6,7
X	BR. J. PHARMAC. vol. 81, no. 4 , 1984 pages 665 - 674 A. BOWMANN ET AL. 'Cyclic GMP mediates neurogenic relaxation in the bovine retractor penis muscle' see page 670 - page 672	9-11
Y		1-5,8
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	AM. J. PHYSIOL. vol. 264 , February 1993 pages H419 - H422 F. TRIGO-ROCHA ET AL. 'Nitric oxide and cGMP: mediators of pelvic nerve-stimulated erection in dogs'	9-11
Y	see page H419 see page H422	1-5,8

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte ...nal Application No
PCT/EP 94/01580

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		JP-A-	6041133	15-02-94
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		NZ-A-	243472	23-12-93
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(54) Title: ISOBUTYLGABA AND ITS DERIVATIVES FOR THE TREATMENT OF PAIN

(57) Abstract

The instant invention is a method of using certain analogs of glutamic acid and gamma-aminobutyric acid in pain therapy.

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ISOBUTYLGABA AND ITS DERIVATIVES FOR THE TREATMENT OF PAIN

BACKGROUND OF THE INVENTION

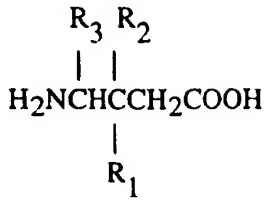
The present invention is the use of analogs of glutamic acid and gamma-aminobutyric acid (GABA) in pain therapy, as the compounds exhibit analgesic/antihyperalgesic action. Advantages of the use of the compounds includes the finding that repeated use does not lead to tolerance nor is there a cross-tolerance between morphine and the compounds.

The compounds of the invention are known agents useful in antiseizure therapy for central nervous system disorders such as epilepsy, Huntington's chorea, cerebral ischemia, Parkinson's disease, tardive dyskinesia, and spasticity. It has also been suggested that the compounds can be used as antidepressants, anxiolytics, and antipsychotics. See WO 92/09560 (United States Serial Number 618,692 filed November 27, 1990) and WP 93/23383 (United States Serial Number 886,080 filed May 20, 1992).

SUMMARY OF THE INVENTION

The instant invention is a method of using a compound of Formula I below in the treatment of pain, especially for treatment of chronic pain disorders. Such disorders include, but are not limited to, inflammatory pain, postoperative pain, osteoarthritis pain associated with metastatic cancer, trigeminal neuralgia, acute herpetic and postherpetic neuralgia, diabetic neuropathy, causalgia, brachial plexus avulsion, occipital neuralgia, reflex sympathetic dystrophy, fibromyalgia, gout, phantom limb pain, burn pain, and other forms of neuralgic, neuropathic, and idiopathic pain syndromes.

A compound are those of Formula I



I

or a pharmaceutically acceptable salt thereof wherein

R_1 is a straight or branched alkyl of from 1 to 6 carbon atoms, phenyl, or cycloalkyl of from 3 to 6 carbon atoms;

R_2 is hydrogen or methyl; and

R_3 is hydrogen, methyl, or carboxyl.

Diastereomers and enantiomers of compounds of Formula I are included in the invention.

Preferred compounds of the invention are those according to Claim 1 wherein R_3 and R_2 are hydrogen, and R_1 is $-(CH_2)_{0-2}$-i C_4H_9 as an (R), (S), or (R,S) isomer.

The more preferred compounds of the invention are (S)-3-(aminomethyl)-5-methylhexanoic acid and 3-aminomethyl-5-methyl-hexanoic acid.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1. Effect of Gabapentin (1-(aminomethyl)-cyclohexaneacetic acid), CI-1008 ((S)-3-(aminomethyl)-5-methylhexanoic acid), and 3-aminomethyl-5-methyl-hexanoic acid in the Rat Paw Formalin Test

Test compounds were administered s.c. 1 hour before an intraplantar injection of 50 µL formalin. The time spent licking/biting the injected paw during the early and late phases was scored. Results are shown as the mean ±SEM of 6 to 8 animals per group. *P <0.05 and **P <0.01 significantly different from vehicle (Veh.) treated controls (ANOVA followed by Dunnett's t-test).

Figure 2. Effect of Gabapentin and CI-1008 on Carrageenin-Induced Mechanical Hyperalgesia

Nociceptive pressure thresholds were measured in the rat using the paw pressure test. Baseline (BL) measurements were taken before animals were administered with 100 µL of 2% carrageenin by intraplantar injection. Results are shown as mean (±SEM) of 8 animals per group. Gabapentin (GP), CI-1008, or morphine (MOR; 3 mg/kg) was administered s.c. 3.5 hours after carrageenin. *P <0.05 and **P <0.01 significantly different from vehicle control group at the same time point (ANOVA followed by Dunnett's t-test).

Figure 3. Effect of Gabapentin and CI-1008 on Carrageenin-Induced Thermal Hyperalgesia

Nociceptive thermal thresholds were measured in the rat using the Hargreaves apparatus. Baseline (BL) measurements were taken before animals were administered with 100 µL of 2% carrageenin by intraplantar injection. Results are shown as mean (±SEM) of 8 animals per group. Gabapentin (GP) or CI-1008 was administered s.c. 2.5 hours after carrageenin. *P <0.05 and **P <0.01 significantly different from vehicle control group at the same time point (ANOVA followed by Dunnett's t-test).

Figure 4. Effect of (a) Morphine, (b) Gabapentin, and (c) S-(+)-3-Isobutylgaba on Thermal Hyperalgesia in the Rat Postoperative Pain Model

Gabapentin or S-(+)-3 isobutylgaba was administered 1 hour before surgery. Morphine was administered 0.5 hour before surgery. Thermal paw withdrawal latencies (PWL) were determined for both ipsilateral and contralateral paws using the rat plantar test. For clarity contralateral paw data for drug-treated animals is not shown. Baseline (BL) measurements were taken before surgery and PWL were reassessed 2, 24, 48, and 72 hours postsurgery. Results are expressed as the mean PWL(s) of 8 to 10 animals per group (vertical bars reperesent ±SEM). *P <0.05 **P <0.01 significantly different (ANOVA followed by Dunnett's t-test), comparing ipsilateral paw of drug-treated groups to ispsilateral paw of vehicle-treated group at each time point. In the figure, -●- is vehicle contralateral,

-O- is vehicle ispsilateral, -Δ- is 1 mg/kg morphine, -□- is 3, and -◇- is 6 for morphine in 4a. In 4b, -Δ- is 3, -□- is 10, and -◇- is 30 for gabapentin. In 4c, -Δ- is 3 mg/kg, -□- is 10, and -◇- is 30 for S-(+)- isobutylgaba.

Figure 5 Effect of (a) Morphine, (b) Gabapentin, and (c) S-(+)-3-Isobutylgaba on Tactile Allodynia in the Rat Postoperative Pain Model

Gabapentin or S-(+)-3-isobutylgaba was administered 1 hour before surgery. Morphine was administered 0.5 hour before surgery. Paw withdrawal thresholds to von Frey hair filaments were determined for both ipsilateral and contralateral paws. For clarity, contralateral paw data for drug-treated animals is not shown. Baseline (BL) measurements were taken before surgery, and withdrawal thresholds were reassessed 3, 25, 49, and 73 hours postsurgery. Results are expressed as median force (g) required to induce a withdrawal of paw in 8 to 10 animals per group (vertical bars represent first and third quartiles). *P <0.05 significantly different (Mann Whitney t-test) comparing ipsilateral paw of drug-treated groups to ipsilateral paw of vehicle treated group at each time point. In Figure 5, -●- is vehicle contralateral, -O- is vehicle ispsilateral. For morphine (5a), -Δ- is 1 mg/kg, -□- is 3, and -◇- is 16.

In 5b for gabapentin and S-(+)-isobutylgaba, -Δ- is 3 mg/kg, -□- is 10, and -◇- is 30.

Figure 6. Effect of S-(+)-3-Isobutylgaba on the Maintenance of (a) Thermal Hyperalgesia and (b) Tactile Allodynia in the Rat Postoperative Pain Model.

S-(+)-3-Isobutylgaba (S-(+)-IBG) was administered 1 hour after surgery. Thermal paw withdrawal latencies, determined using the rat plantar test, and paw withdrawal thresholds to von Frey hair filaments, were determined in separate groups of animals for both ipsilateral and contralateral paws. For clarity only the ipsilateral paw data is shown. Baseline (BL) measurements were taken before surgery and withdrawal thresholds were reassessed up to 6 hours postsurgery. For thermal hyperalgesia, the results are expressed as the mean PWL(s) of 6 animals per group (vertical bars represent ±SEM), *P <0.05 **P <0.01 significantly

different (unpaired t-test), comparing ipsilateral paw of drug-treated group to ipsilateral paw of vehicle (Veh -O-) treated group at each time point. For tactile allodynia, the results are expressed as median force (g) required to induce a paw withdrawal of 6 animals per group (vertical bars represent first and third quartiles). *P <0.05 significantly different (Mann Whitney t-test), comparing ipsilateral paw of drug-treated group to ipsilateral paw of vehicle-treated group at each time point. -●- is S-(+)-IBG at 30 mg/kg.

DETAILED DESCRIPTION

The instant invention is a method of using a compound of Formula I above as an analgesic in the treatment of pain as listed above. Pain such as inflammatory pain, neuropathic pain, cancer pain, postoperative pain, and idiopathic pain which is pain of unknown origin, for example, phantom limb pain are included especially. Neuropathic pain is caused by injury or infection of peripheral sensory nerves. It includes, but is not limited to pain from peripheral nerve trauma, herpes virus infection, diabetes mellitus, causalgia, plexus avulsion, neuroma, limb amputation, and vasculitis. Neuropathic pain is also caused by nerve damage from chronic alcoholism, human immunodeficiency virus infection, hypothyroidism, uremia, or vitamin deficiencies. Neuropathic pain includes, but is not limited to pain caused by nerve injury such as, for example, the pain diabetics suffer from.

The conditions listed above are known to be poorly treated by currently marketed analgesics such as narcotics or nonsteroidal anti-inflammatory drugs (NSAID) due to insufficient efficacy or limiting side effects.

The terms used in Formula I are, for example, alkyl which term is methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, isopentyl, and neopentyl, as well as those as would occur to one skilled in the art.

The term "cycloalkyl" is exemplified by cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

The compounds of the present invention may form pharmaceutically acceptable salts with both organic and inorganic acids or bases. For example, the

acid addition salts of the basic compounds are prepared either by dissolving the free base in aqueous or aqueous alcohol solution or other suitable solvents containing the appropriate acid and isolating the salt by evaporating the solution. Examples of pharmaceutically acceptable salts are hydrochlorides, hydrobromides, hydrosulfates, etc. as well as sodium, potassium, and magnesium, etc. salts.

The compounds of the present invention can contain one or several asymmetric carbon atoms. The invention includes the individual diastereomers or enantiomers, and the mixtures thereof. The individual diastereomers or enantiomers may be prepared or isolated by methods already well-known in the art.

The method for the formation of the 3-alkyl-4-aminobutanoic acids starting from 2-alkenoic esters is prepared from commercially available aldehydes and monoethyl malonate by the Knoevenagel reaction (Kim Y.C., Cocolase G.H., J. Med. Chem., 1965:8509), with the exception of ethyl 4,4-dimethyl-2-pentenoate. This compound was prepared from 2,2-dimethylpropanal and ethyl lithioacetate, followed by dehydration of the β-hydroxyester with phosphoryl chloride and pyridine. The Michael addition of nitromethane to α, β-unsaturated compounds mediated by 1,1,3,3-tetramethylguanidine or 1,8-diazabicyclo[5.4.0]undec-7-ene(DBU) afforded 4-nitroesters in good yields.

Although the aliphatic nitro compounds are usually reduced by either high pressure catalytic hydrogenation by metal-catalyzed transfer hydrogenation, or by newly introduced hydrogenolysis methods with ammonium formate or sodium borohydride and palladium as catalysts, applicants have found that 4-nitrocarboxylic esters can be reduced almost quantitatively to the corresponding 4-aminocarboxylic esters by hydrogenation using 10% palladium on carbon as catalysts in acetic acid at room temperature and atmospheric pressure. The amino esters produced were subjected to acid hydrolysis to afford the subject inventive compounds in good yields. This procedure provides access to a variety of 3-alkyl-4-aminobutanoic acids as listed in Tables 1 and 2 as examples, and thus is advantageous in comparison to methods previously used.

When the starting material is not commercially available, the synthetic sequence was initiated with the corresponding alcohol, which was oxidized to the aldehyde by the method of Corey, et al., Tetrahedrom. Lett., 1975:2647-2650.

The compounds made by the synthetic methods can be used as pharmaceutical compositions as agent in the treatment of pain when an effective amount of a compound of the Formula I, together with a pharmaceutically acceptable carrier is used. The pharmaceutical can be used in a method for treating such disorders in mammals, including human, suffering therefrom by administering to such mammals an effective amount of the compound as described above in unit dosage form.

The pharmaceutical compound, made in accordance with the present invention, can be prepared and administered in a wide variety of dosage forms by either oral or parenteral routes of administration. For example, these pharmaceutical compositions can be made in inert, pharmaceutically acceptable carriers which are either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets, and suppositories. Other solid and liquid form preparations could be made in accordance with known methods of the art and administered by the oral route in an appropriate formulation, or by a parenteral route such as intravenous, intramuscular, or subcutaneous injection as a liquid formulation.

The quantity of active compound in a unit dose of preparation may be varied or adjusted from 1 mg to about 300 mg/kg daily, based on an average 70-kg patient. A daily dose range of about 1 mg to about 50 mg/kg is preferred. The dosages, however, may be varied depending upon the requirement with a patient, the severity of the condition being treated, and the compound being employed. Determination of the proper dosage for particular situations is within the skill of the art.

Effects of Gabapentin, CI-1008, and 3-Aminomethyl-5-methyl-hexanoic Acid in the Rat Formalin Paw Test

Male Sprague-Dawley rats (70-90 g) were habituated to perspex observation chambers (24 cm × 24 cm × 24 cm) for at least 15 minutes prior to

testing. Formalin-induced hind paw licking and biting was initiated by a 50 µL subcutaneous injection of a 5% formalin solution (5% formaldehyde in isotonic saline) into the plantar surface of the left hind paw. Immediately following the formalin injection, licking/biting of the injected hind paw was scored in 5 minute bins for 60 minutes. The results are expressed as mean combined licking/biting time for the early phase (0-10 minutes) and late phase (10-45 minutes).

The s.c. administration of gabapentin (10-300 mg/kg) or CI-1008 (1-100 mg/kg) 1 hour before formalin dose-dependently blocked the licking/biting behavior during the late phase of the formalin response with respective minimum effective doses (MED) of 30 and 10 mg/kg (Figure 1). However, neither of the compounds affected the early phase at any of the doses tested. Similar administration of 3-aminomethyl-5-methyl-hexanoic acid produced only a modest blockade of the late phase at 100 mg/kg.

Effects of Gabapentin and CI-1008 on Carrageenin-Induced Hyperalgesia

On the test Day, 2 to 3 baseline measurements were taken before rats (male Sprague-Dawley 70-90 g) were administered with 100 µL of 2% carrageenin by intraplantar injection into the right hind paw. Animals were dosed with the test drug after development of peak hyperalgesia. Separate groups of animals were used for the mechanical and thermal hyperalgesia studies.

A. Mechanical Hyperalgesia

Nociceptive pressure thresholds were measured in the rat paw pressure test using an analgesimeter (Ugo Basile). A cut-off point of 250 g was used to prevent any damage to the paw. The intraplantar injection of carrageenin produced a reduction in the nociceptive pressure threshold between 3 and 5 hours after injection, indicating induction of hyperalgesia. Morphine (3 mg/kg, s.c.) produced a complete blockade of hyperalgesia (Figure 2). Gabapentin (3-300 mg/kg, s.c.) and CI-1008 (1-100 mg/kg, s.c.) dose-dependently antagonized the hyperalgesia, with respective MED of 10 and 3 mg/kg (Figure 2).

B. Thermal Hyperalgesia

Baseline paw withdrawal latencies (PWL) were obtained for each rat using the Hargreaves model. Carrageenin was injected as described above. Animals were then tested for thermal hyperalgesia at 2 hours postcarrageenin administration. Gabapentin (10-100 mg/kg) or CI-1008 (1-30 mg/kg) was administered s.c. 2.5 hours after carrageenin, and PWL were re-evaluated at 3 and 4 hours postcarrageenin administration. Carrageenin induced a significant reduction in paw withdrawal latency at 2, 3, and 4 hours following injection, indicating the induction of thermal hyperalgesia (Figure 3). Gabapentin and CI-1008 dose-dependently antagonized the hyperalgesia with a MED of 30 and 3 mg/kg (Figure 3).

These data show that gabapentin and CI-1008 are effective in the treatment of inflammatory pain.

The assay of Bennett G.J. provides an animal model of a peripheral mononeuropathy in rat that produces disorder of pain sensation like those seen in man (Pain, 1988;33:87-107).

The assay of Kim S.H., et al., provides one experimental model for peripheral neuropathy produced by segmented spinal nerve ligation in the rat (Pain, 1990;50:355-363).

A rat model of postoperative pain has been described (Brennan et al., 1996). It involves an incision of the skin, fascia, and muscle of the plantar aspect of the hind paw. This leads to an induction of reproducible and quantifiable mechanical hyperalgesia lasting several days. It has been suggested that this model displays some similarities to the human postoperative pain state. In the present study we have examined and compared the activities of gabapentin and S-(+)-3-isobutylgaba with morphine in this model of postoperative pain.

METHODS

Male Sprague-Dawley rats (250-300 g), obtained from Bantin and Kingmen, (Hull, U.K.) were used in all experiments. Before surgery, animals were housed in groups of 6 under a 12-hour light/dark cycle (lights on at 07 hour

00 minute) with food and water ad libitum. Postoperatively, animals were housed in pairs on "Aqua-sorb" bedding consisting of air laid cellulose (Beta Medical and Scientific, Sale, U.K.) under the same conditions. All experiments were carried out by an observer blind to drug treatments.

Surgery

Animals were anaesthetized with 2% isofluorane and 1.4 O_2/NO_2 mixture which was maintained during surgery via a nose cone. The plantar surface of the right hind paw was prepared with 50% ethanol, and a 1-cm longitudinal incision was made through skin and fascia, starting 0.5 cm from the edge of the heel and extending towards the toes. The plantaris muscle was elevated using forceps and incised longitudinally. The wound was closed using two simple sutures of braided silk with a FST-02 needle. The wound site was covered with Terramycin spray and Auromycin powder. Postoperatively, none of the animals displayed any signs of infection with the wounds healing well after 24 hours. The sutures were removed after 48 hours.

Evaluation of Thermal Hyperalgesia

Thermal hyperalgesia was assessed using the rat plantar test (Ugo Basile, Italy) following a modified method of Hargreaves, et al., 1988. Rats were habituated to the apparatus which consisted of three individual perspex boxes on an elevated glass table. A mobile radiant heat source was located under the table and focused onto the hind paw and paw withdrawal latencies (PWL) were recorded. There was an automatic cut off point of 22.5 seconds to prevent tissue damage. PWLs were taken 2 to 3 times for both hind paws of each animal, the mean of which represented baselines for right and left hind paws. The apparatus was calibrated to give a PWL of approximately 10 seconds. PWL(s) were reassessed following the same protocol as above 2, 24, 48, and 72 hours postoperatively.

Evaluation of Tactile Allodynia

Tactile allodynia was measured using Semmes-Weinstein von Frey hairs (Stoelting, Illinois, U.S.A.). Animals were placed into wire-mesh-bottom cages allowing access to the underside of their paws. The animals were habituated to this environment prior to the start of the experiment. Tactile allodynia was tested by touching the plantar surface of the animals hind paw with von Frey hairs in ascending order of force (0.7, 1.2, 1.5, 2, 3.6, 5.5, 8.5, 11.8, 15.1, and 29 g) until a paw withdrawal response was elicited. Each von Frey hair was applied to the paw for 6 seconds, or until a response occurred. Once a withdrawal response was established, the paw was retested, starting with the next descending von Frey hair until no response occurred. The highest force of 29 g lifted the paw as well as eliciting a response, thus represented the cut-off point. Each animal had both hind paws tested in this manner. The lowest amount of force required to elicit a response was recorded as withdrawal threshold in grams. When compounds were administered before surgery, the same animals were used to study drug effects on tactile, allodynia, and thermal hyperalgasia, with each animal being tested for tactile allodynia 1 hour after thermal hyperalgesia. Separate groups of animals were used for examination of tactile allodynia and thermal hyperalgesia when S-(+)-3-isobutylgaba was administered after surgery.

Statistics

Data obtained for thermal hyperalgesia was subjected to a one-way (analysis of variance) ANOVA followed by a Dunnett's t-test. Tactile allodynia results obtained with the von Frey hairs were subjected to an individual Mann Whitney t-test.

RESULTS

An incision of the rat plantaris muscle led to an induction of thermal hyperalgesia and tactile allodynia. Both nociceptive responses peaked within 1 hour following surgery and were maintained for 3 days. During the experimental period, all animals remained in good health.

Effect of Gabapentin, S-(+)-3-Isobutylgaba and Morphine Administered Before Surgery on Thermal Hyperalgesia

The single-dose administration of gabapentin 1 hour before surgery dose-dependently (3-30 mg/kg, s.c.) blocked development of thermal hyperalgesia with a MED of 30 mg/kg (Figure 1b). The highest dose of 30 mg/kg gabapentin prevented the hyperalgesic response for 24 hours (Figure 1b). Similar administration of S-(+)-3-isobutylgaba also dose-dependently (3-30 mg/kg, s.c.) prevented development of thermal hyperalgesia with a MED of 3 mg/kg (Figure 1c). The 30 mg/kg dose of S-(+)-3-isobutylgaba was effective up to 3 days (Figure 1c). The administration of morphine 0.5 hour before surgery dose-dependently (1-6 mg/kg, s.c.) antagonized the development of thermal hyperalgesia with a MED of 1 mg/kg (Figure 1a). This effect was maintained for 24 hours (Figure 1a).

Effects of Gabapentin, S-(+)-3-Isobutylgaba and Morphine Administered Before Surgery on Tactile Allodynia

The effect of drugs on development of tactile allodynia was determined in the same animals used for thermal hyperalgesia above. One hour was allowed between thermal hyperalgesia and tactile allodynia tests. Gabapentin dose-dependently prevented development of tactile allodynia with a MED of 10 mg/kg. The 10 and 30 mg/kg doses of gabapentin were effective for 25 and 49 hours, respectively (Figure 2b). S-(+)-3-Isobutylgaba also dose-dependently (3-30 mg/kg) blocked development of the allodynia response with a MED of 10 mg/kg (Figure 2c). This blockade of the nociceptive response was maintained for 3 days by the 30 mg/kg dose of S-(+)-3-isobutylgaba (Figure 2c.). In contrast, morphine (1-6 mg/kg) only prevented the development of tactile allodynia for 3 hour postsurgery at the highest dose of 6 mg/kg (Figure 2a).

Effect of S-(+)-3-Isobutylgaba Administered 1 Hour After Surgery on Tactile Allodynia and Thermal Hyperalgesia

The allodynia and hyperalgesia peaked within 1 hour in all animals and was maintained for the following 5 to 6 hours. The s.c. administration of 30 mg/kg

S-(+)-3-isobutylgaba 1 hour after surgery blocked the maintenance of tactile allodynia and thermal hyperalgesia for 3 to 4 hours. After this time, both nociceptive responses returned to control levels indicating disappearance of antihyperalgesic and antiallodynic actions (Figure 3).

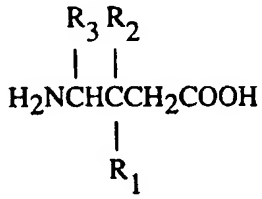
Gabapentin and S-(+)-3-isobutylgaba did not affect PWL in the thermal hyperalgesia test or tactile allodynia scores in the contralateral paw up to the highest dose tested in any of the experiments. In contrast, morphine (6 mg, s.c.) increased PWL of the contralateral paw in the thermal hyperalgesia test (data not shown).

The results presented here show that incision of the rat plantaris muscle induces thermal hyperalgesia and tactile allodynia lasting at least 3 days. The major findings of the present study are that gabapentin and S-(+)-3-isobutylgaba are equally effective at blocking both nociceptive responses. In contrast, morphine was found to be more effective against thermal hyperalgesia than tactile allodynia. Furthermore, S-(+)-3-isobutylgaba completely blocked induction and maintenance of allodynia and hyperalgesia.

CLAIMS

What is claimed is:

1. A method for treating pain comprising administering a therapeutically effective amount of a compound of Formula I



I

or a pharmaceutically acceptable salt, diastereomer, or enantiomer thereof wherein

R_1 is a straight or branched alkyl of from 1 to 6 carbon atoms, phenyl, or cycloalkyl of from 3 to 6 carbon atoms;

R_2 is hydrogen or methyl; and

R_3 is hydrogen, methyl, or carboxyl to a mammal in need of said treatment.

2. A method according to Claim 1 wherein the compound administered is a compound of Formula I wherein R_3 and R_2 are hydrogen, and R_1 is $-(CH_2)_{0-2}$-i C_4H_9 as an (R), (S), or (R,S) isomer.

3. A method according to Claim 1 wherein the compound administered is named (S)-3-(aminomethyl)-5-methylhexanoic acid and 3-aminomethyl-5-methyl-hexanoic acid.

4. A method according to Claim 1 wherein the pain treated is inflammatory pain.

5. A method according to Claim 1 wherein the pain treated is neuropathic pain.

6. A method according to Claim 1 wherein the pain treated is cancer pain.

7. A method according to Claim 1 wherein the pain treated is postoperative pain.

8. A method according to Claim 1 wherein the pain treated is phantom limit pain.

9. A method according to Claim 1 wherein the pain treated is burn pain.

10. A method according to Claim 1 wherein the pain treated is gout pain.

11. A method according to Claim 1 wherein the pain treated is osteoarthritic pain.

12. A method according to Claim 1 wherein the pain treated is trigeminal neuralgia pain.

13. A method according to Claim 1 wherein the pain treated is acute herpetic and postherpetic pain.

14. A method according to Claim 1 wherein the pain treated is causalgia pain.

15. A method according to Claim 1 wherein the pain treated is idiopathic pain.

FIG-1a GABAPENTIN

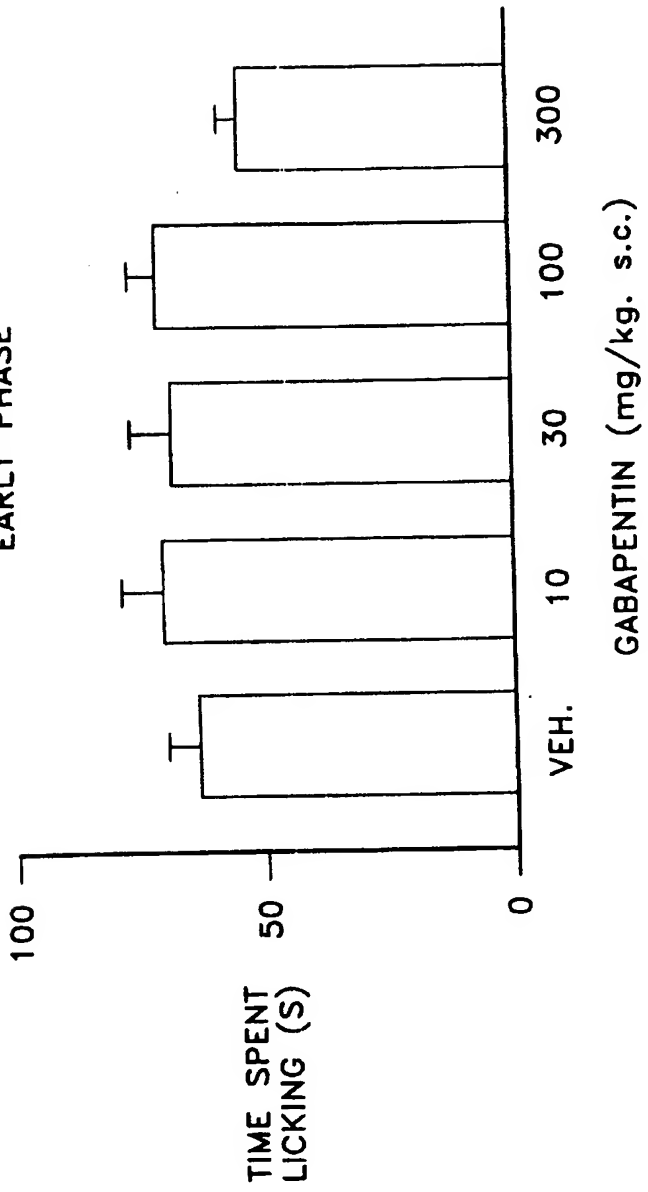


FIG-1b GABAPENTIN

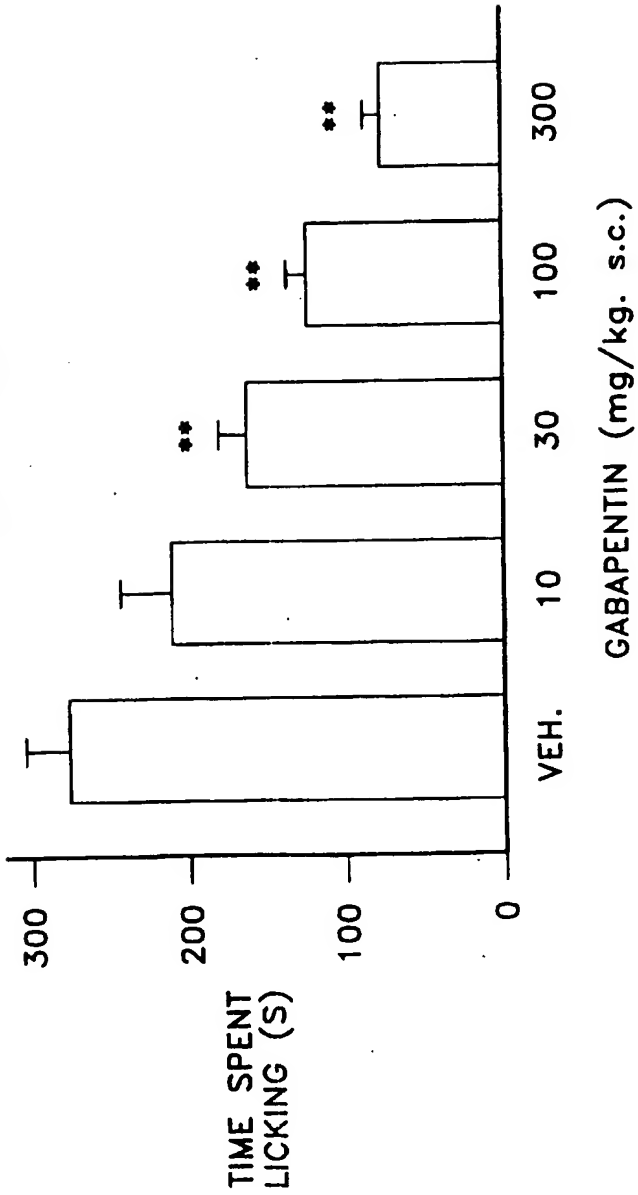


FIG-1C CI-1008

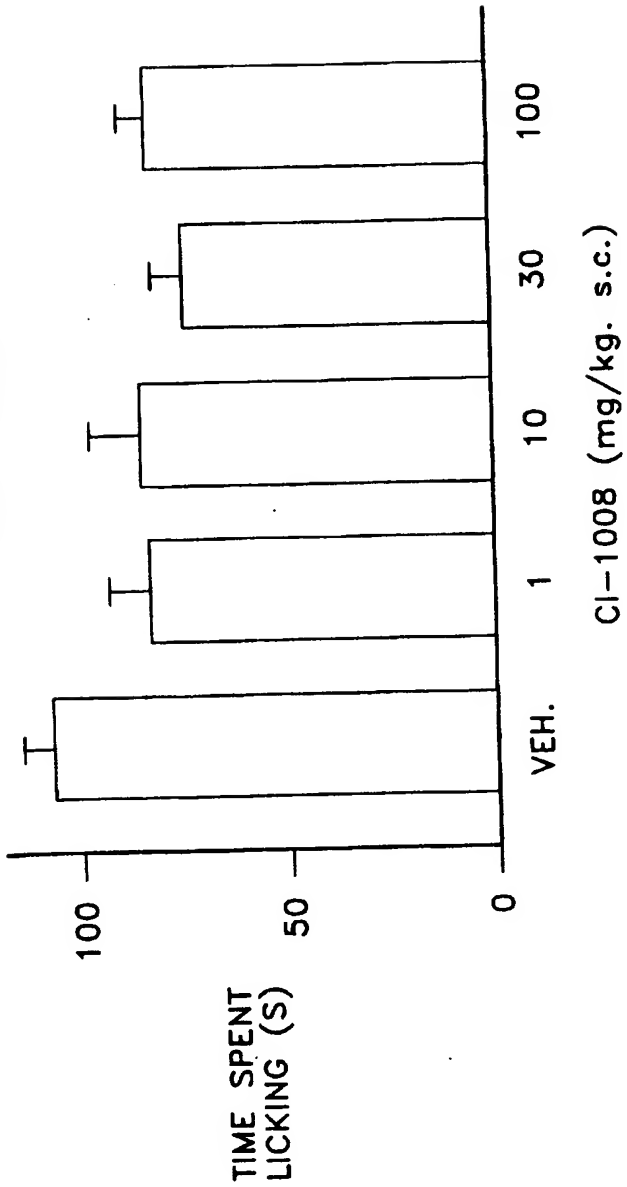


FIG-1d CI-1008

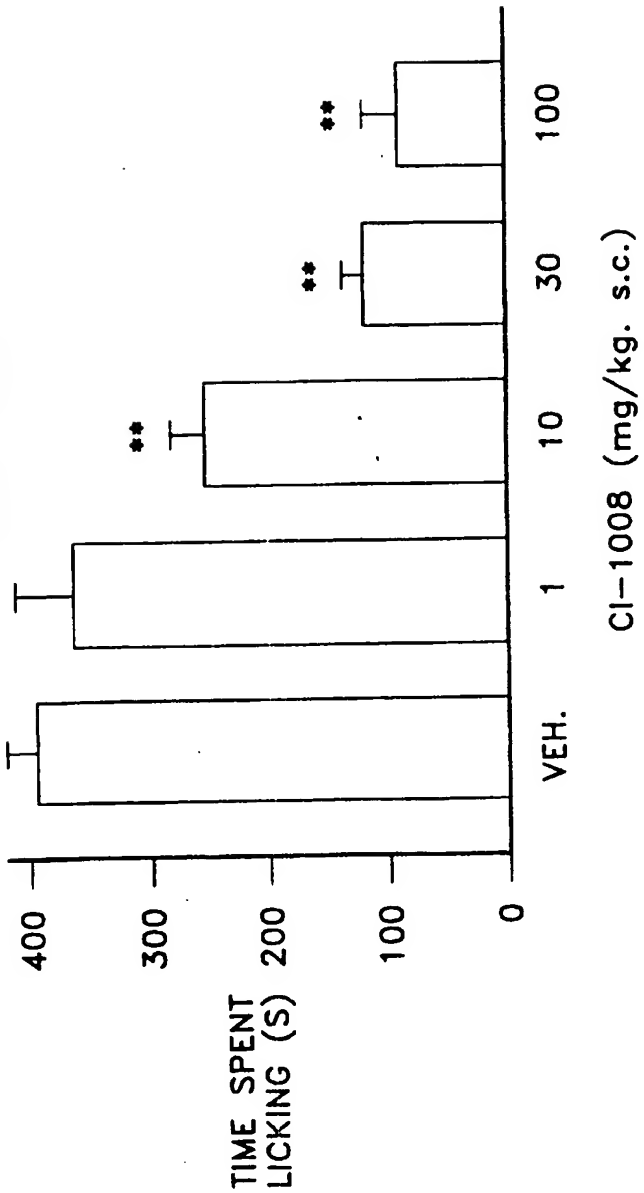


FIG-1e PD 144550

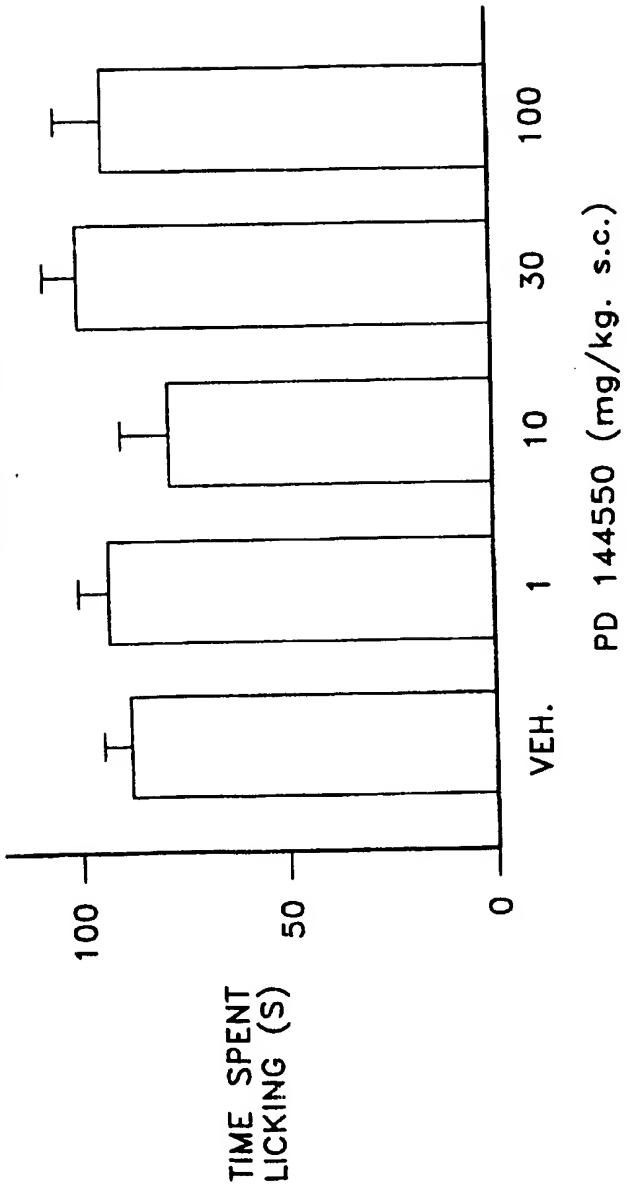


FIG-1f PD 144550

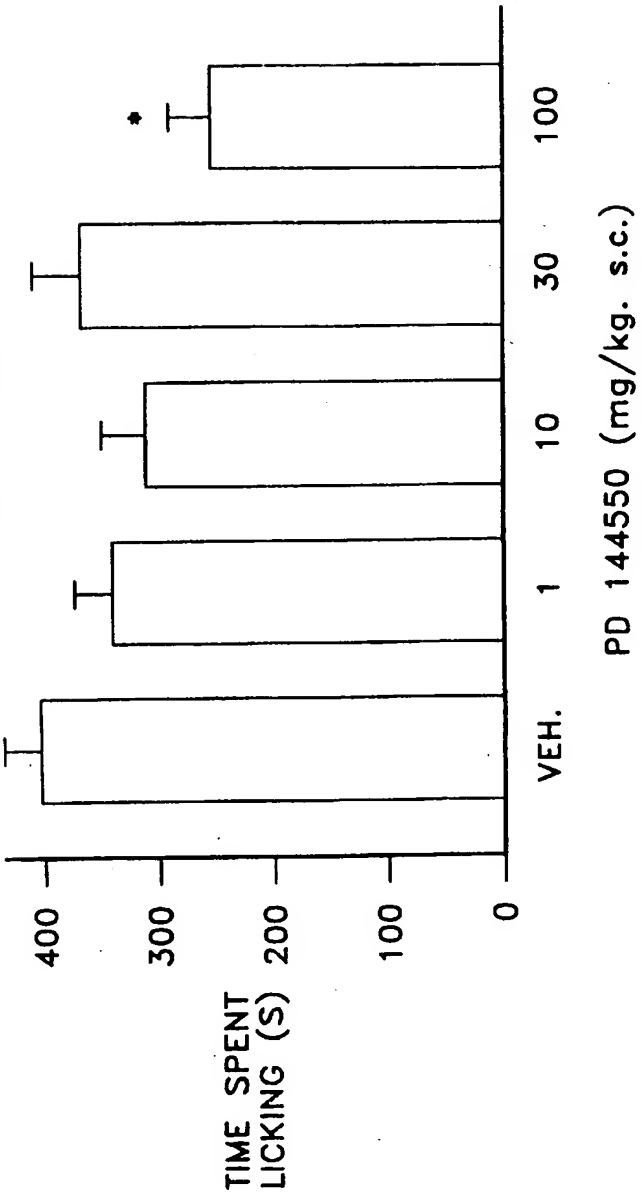
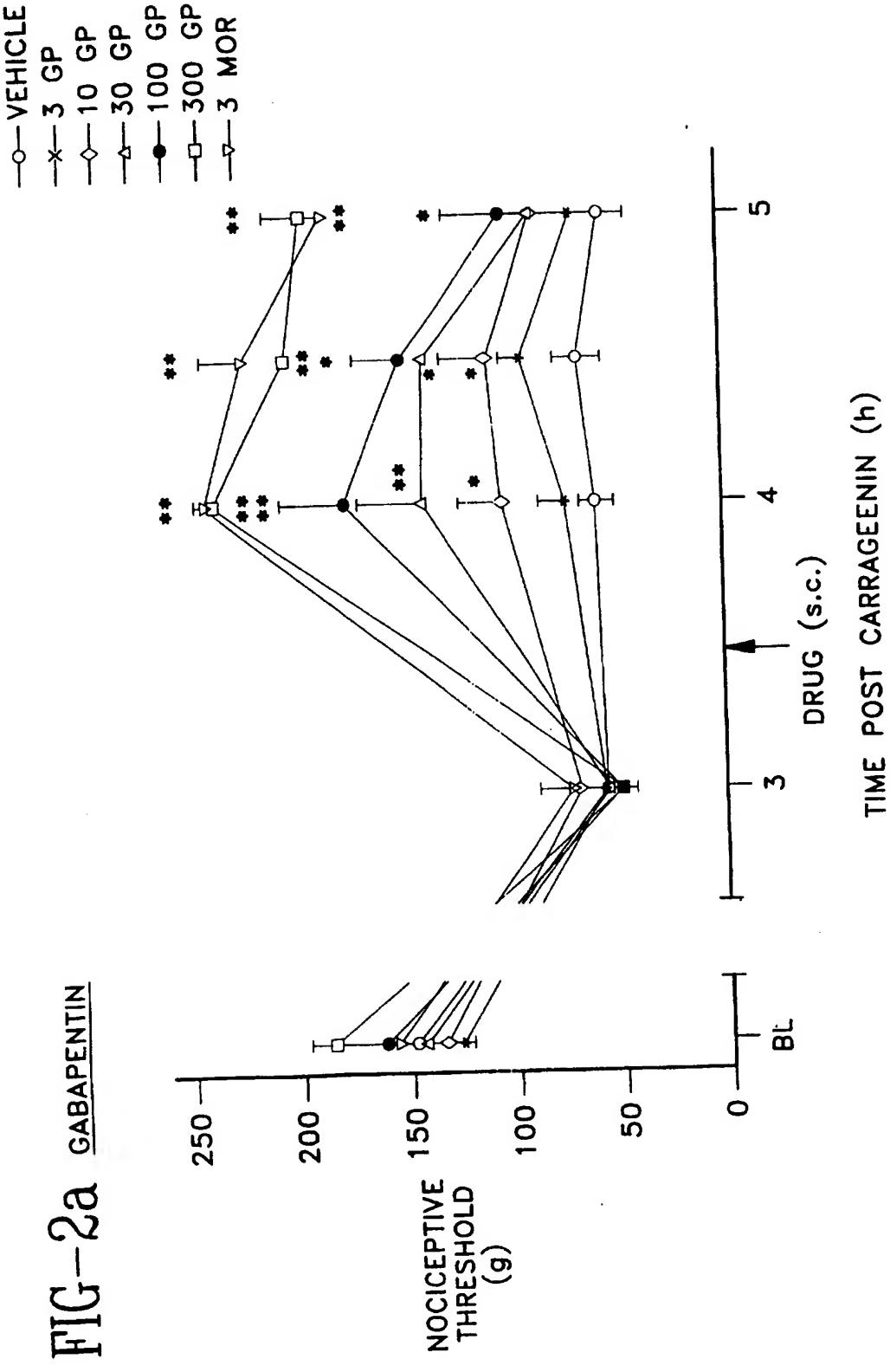


FIG-2a GABAPENTIN



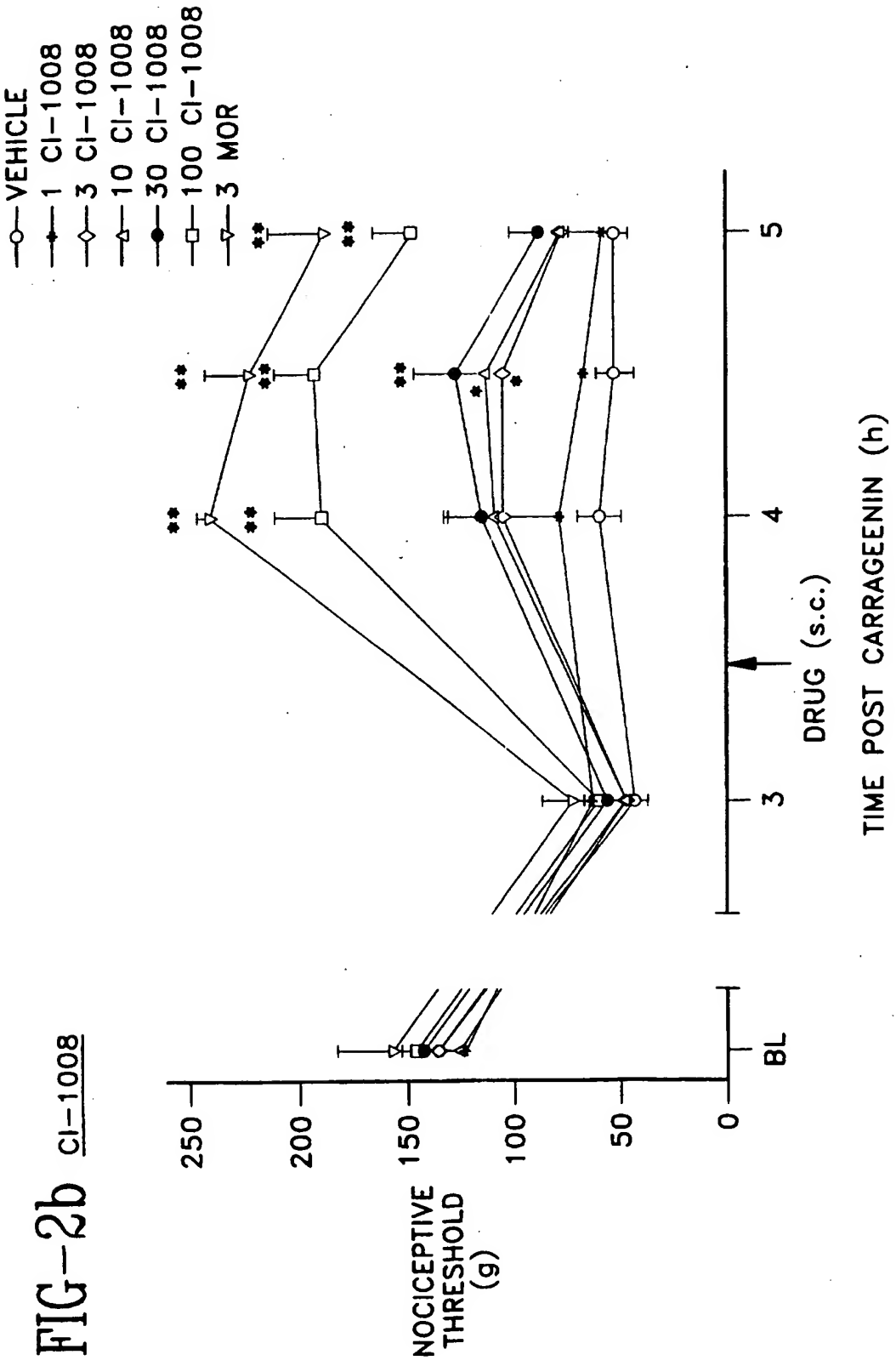


FIG-2b CI-1008

FIG-3a GABAPENTIN

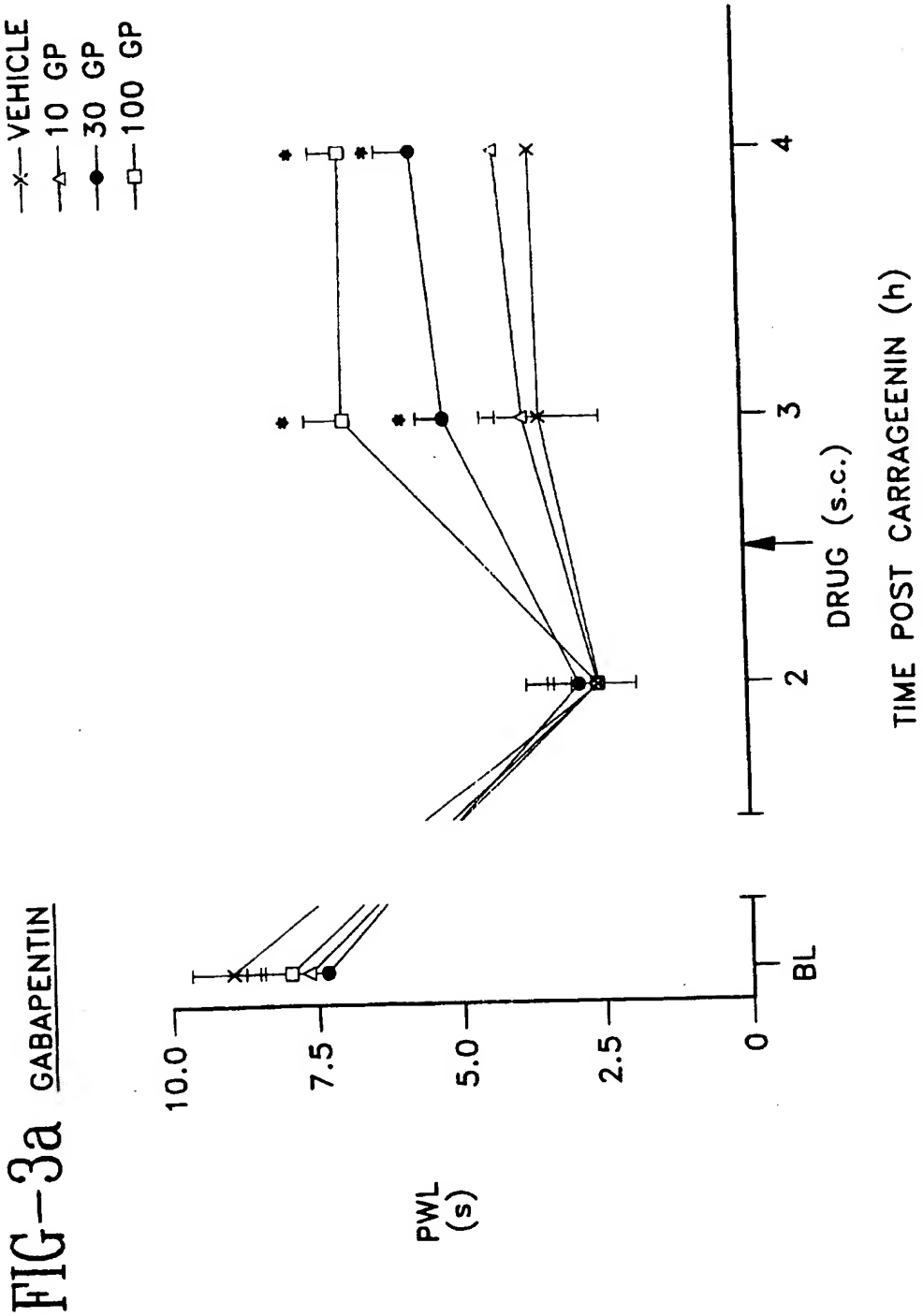


FIG-3b CI-1008

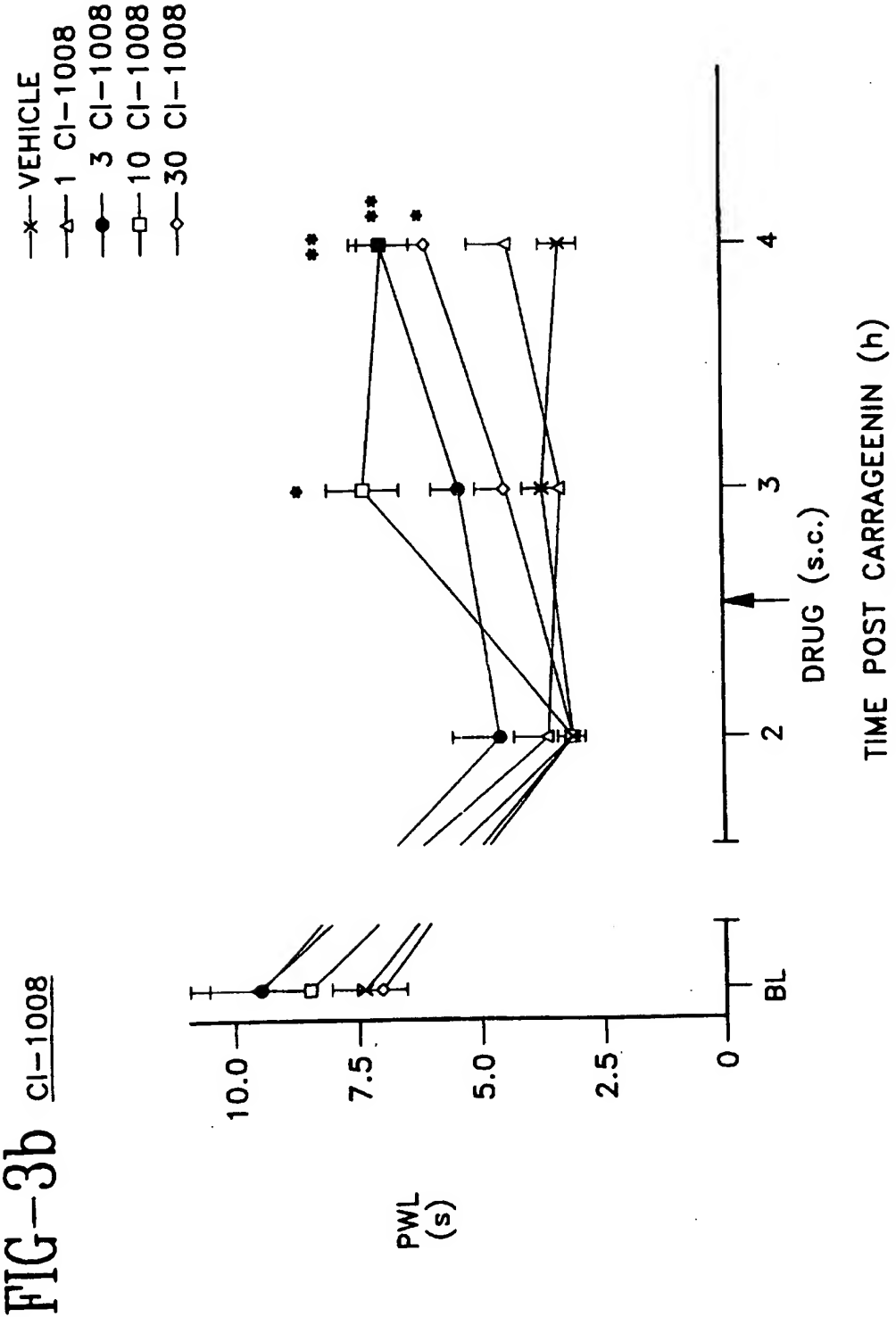
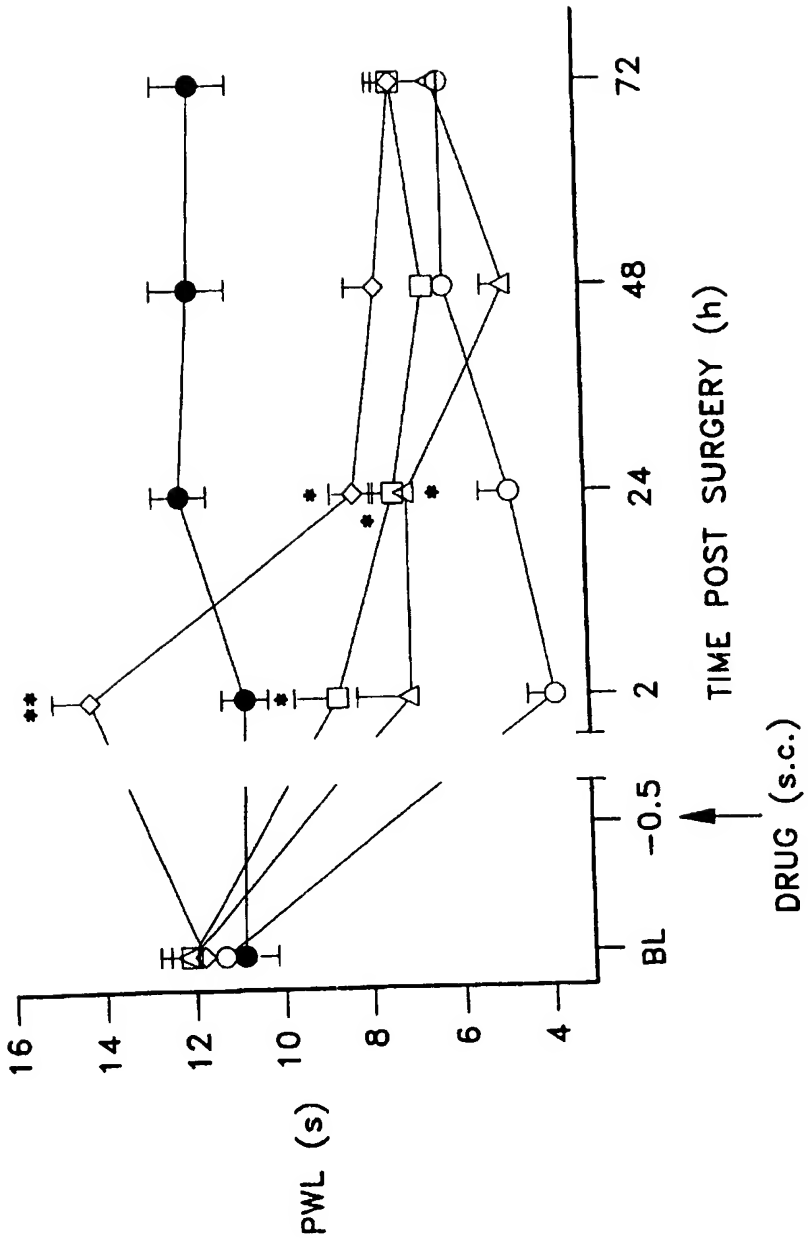


FIG-4a



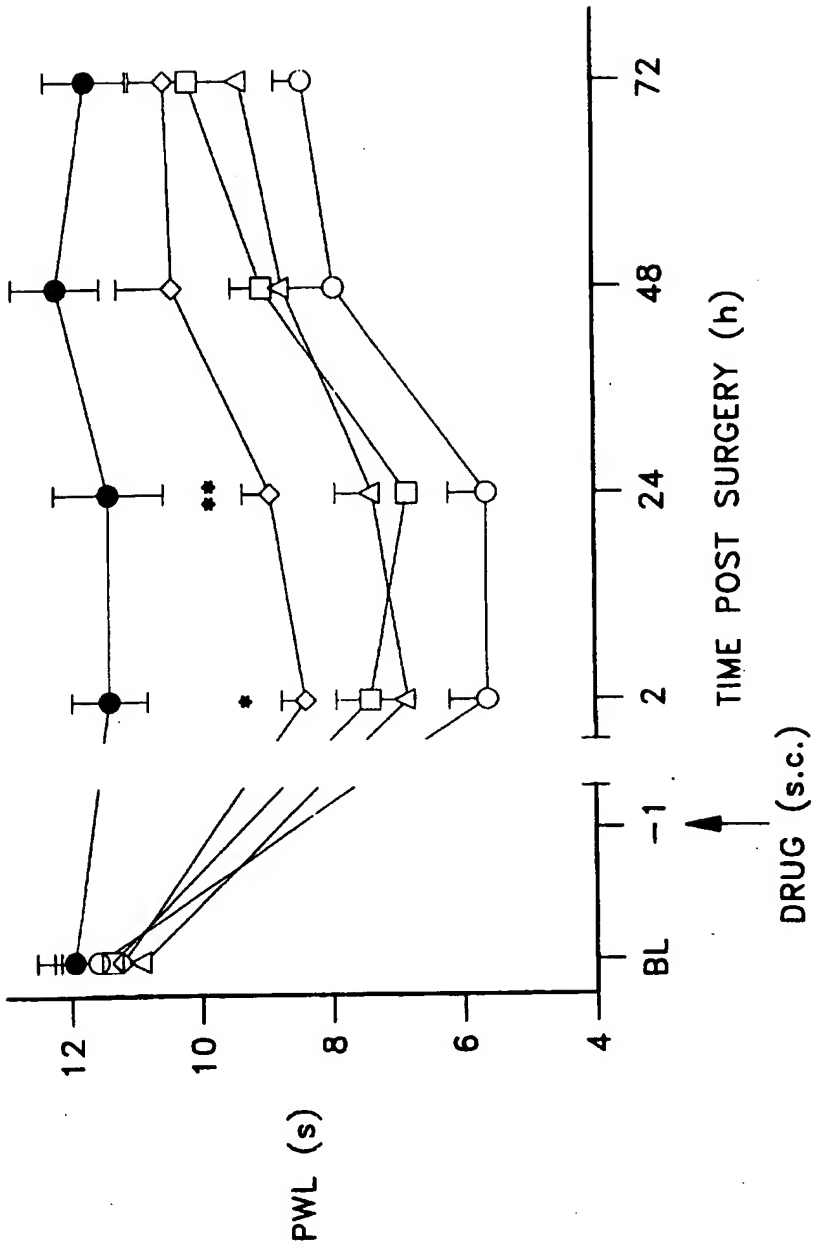


FIG-4b

FIG-4c

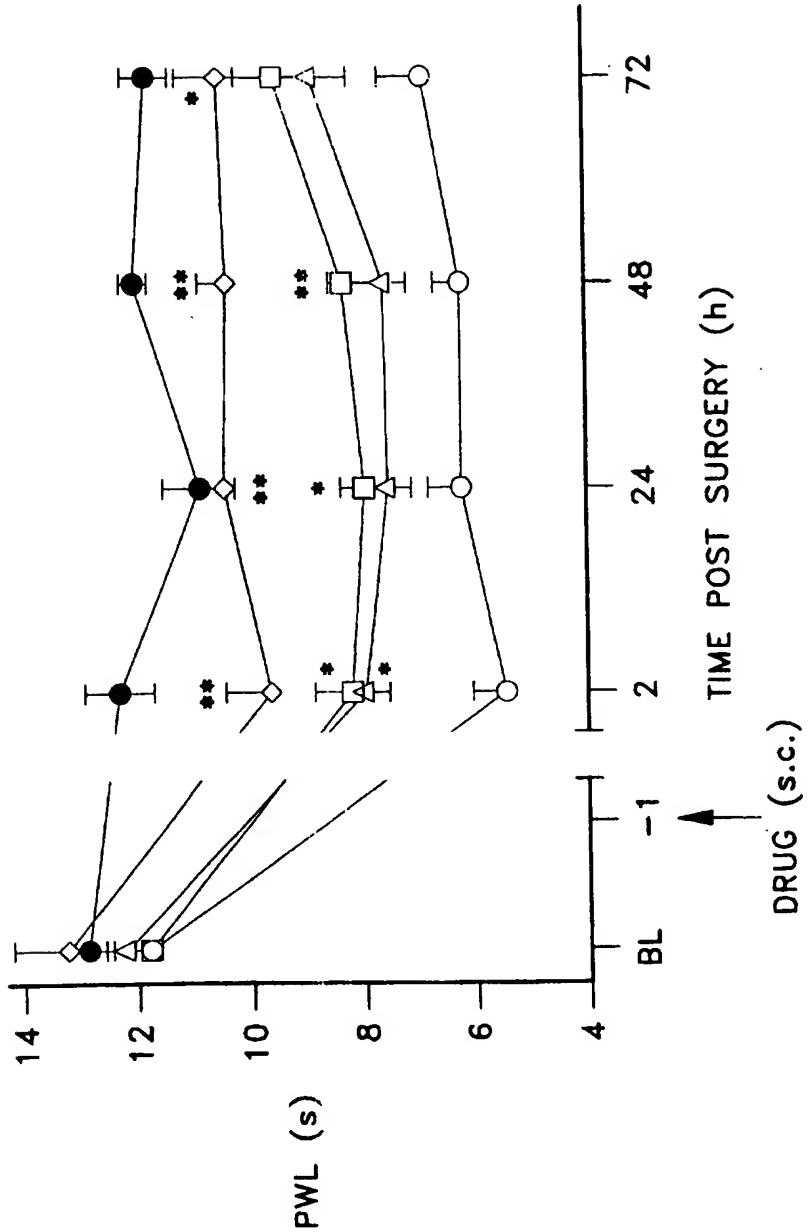
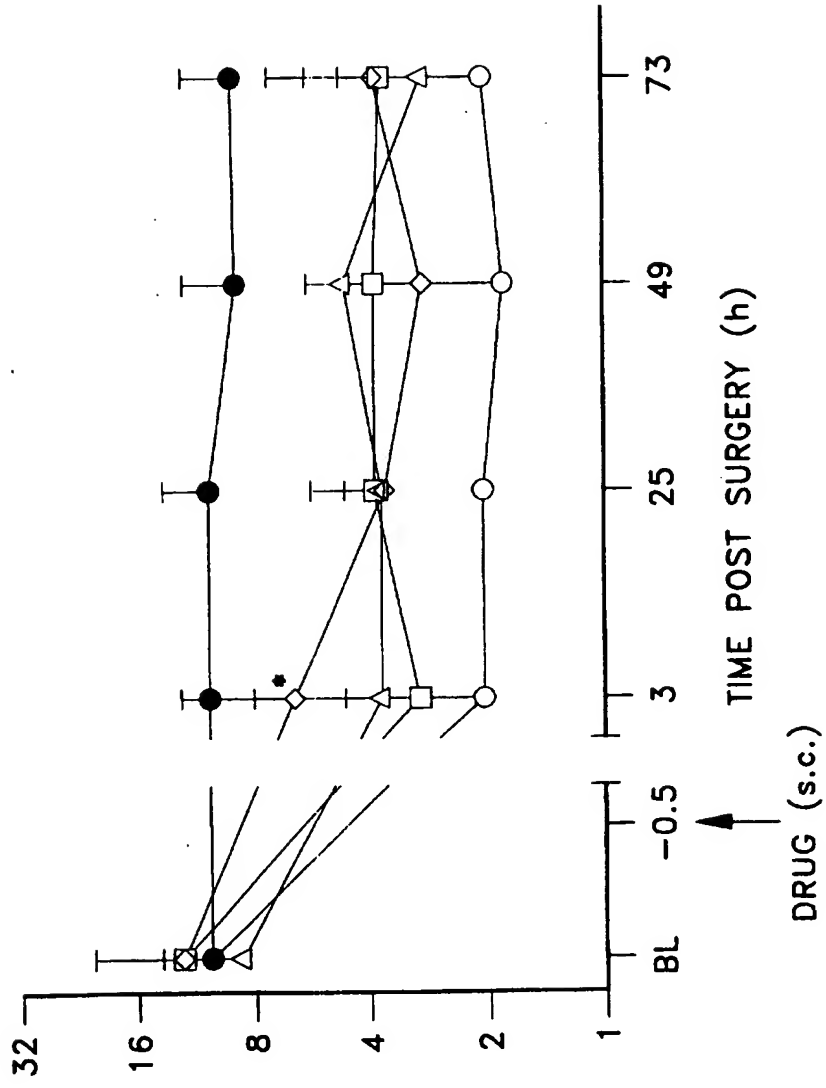


FIG-5a


WITHDRAWAL THRESHOLD (g)
32
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BL
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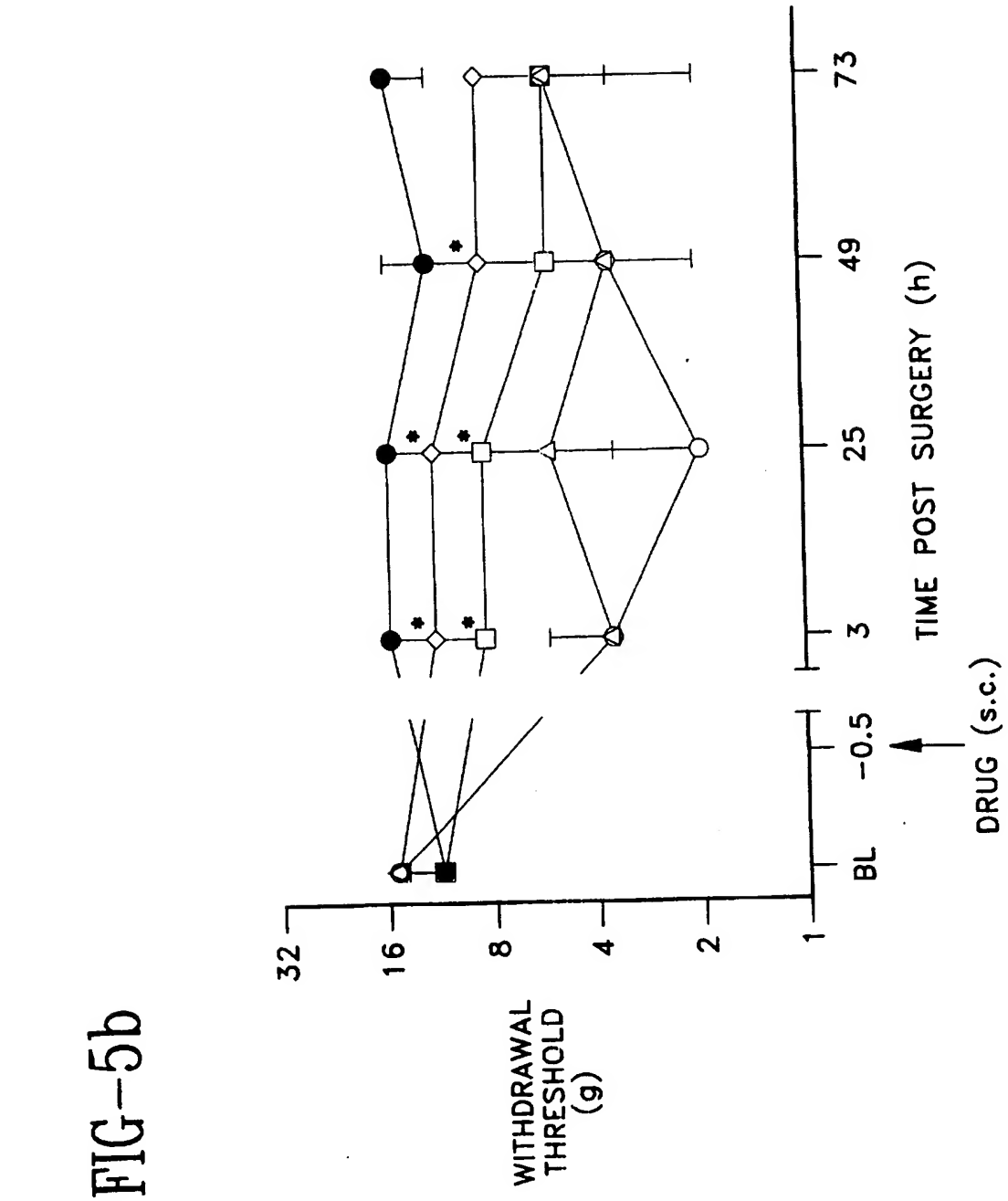
73
TIME POST SURGERY (h)
DRUG (s.c.)
*

FIG-5b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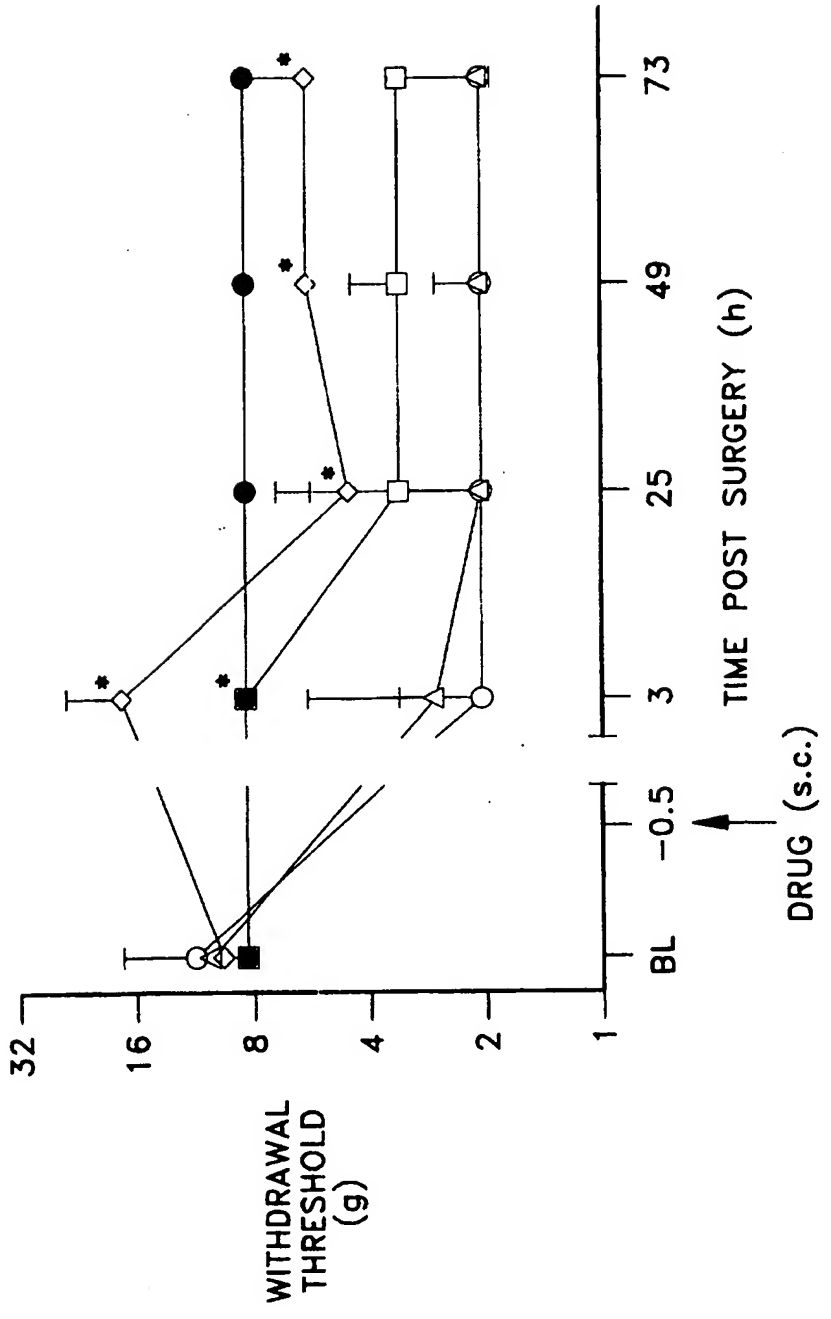
TIME POST SURGERY (h)
DRUG (s.c.)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TIME POST SURGERY (h)

FIG-5C

FIG-6a

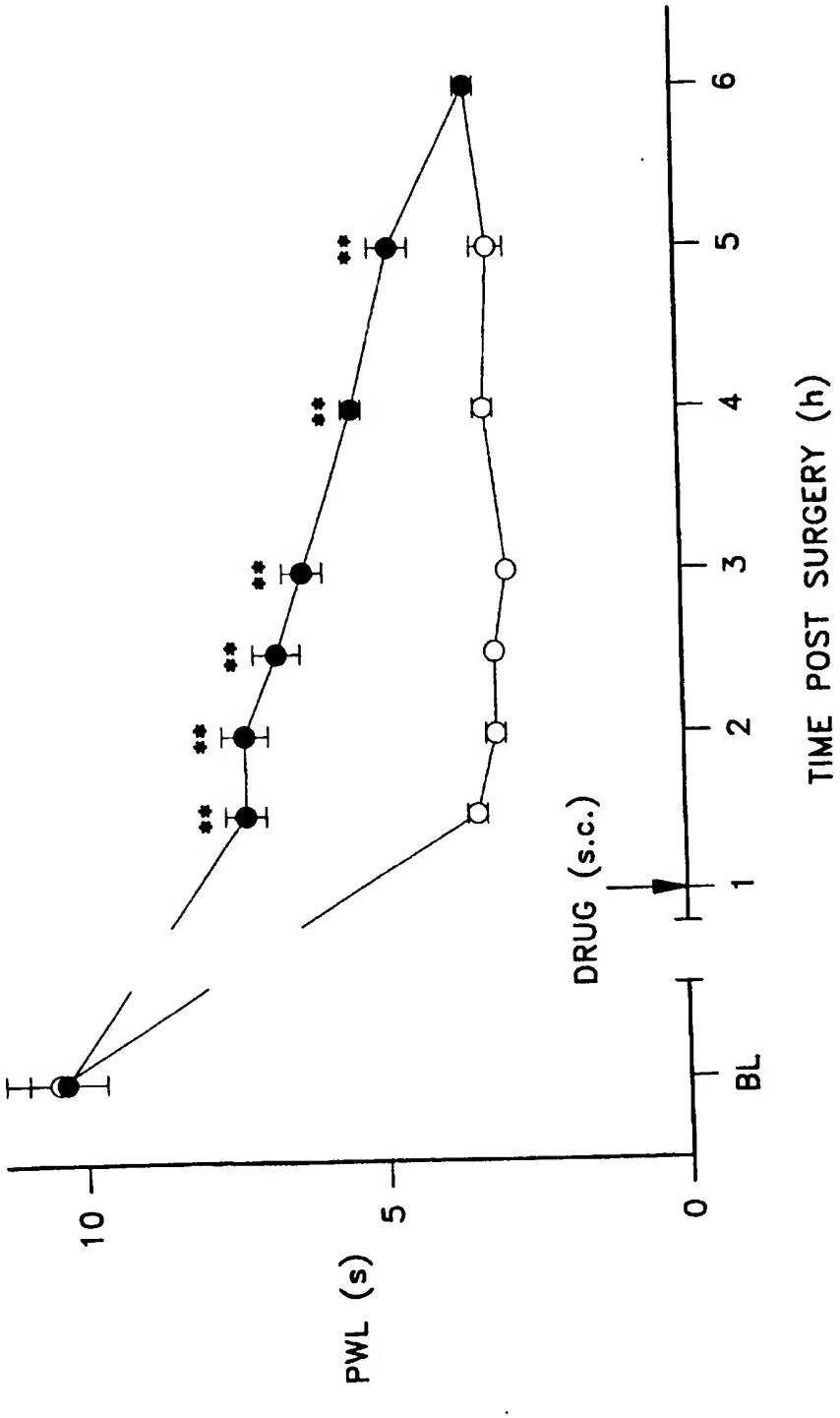
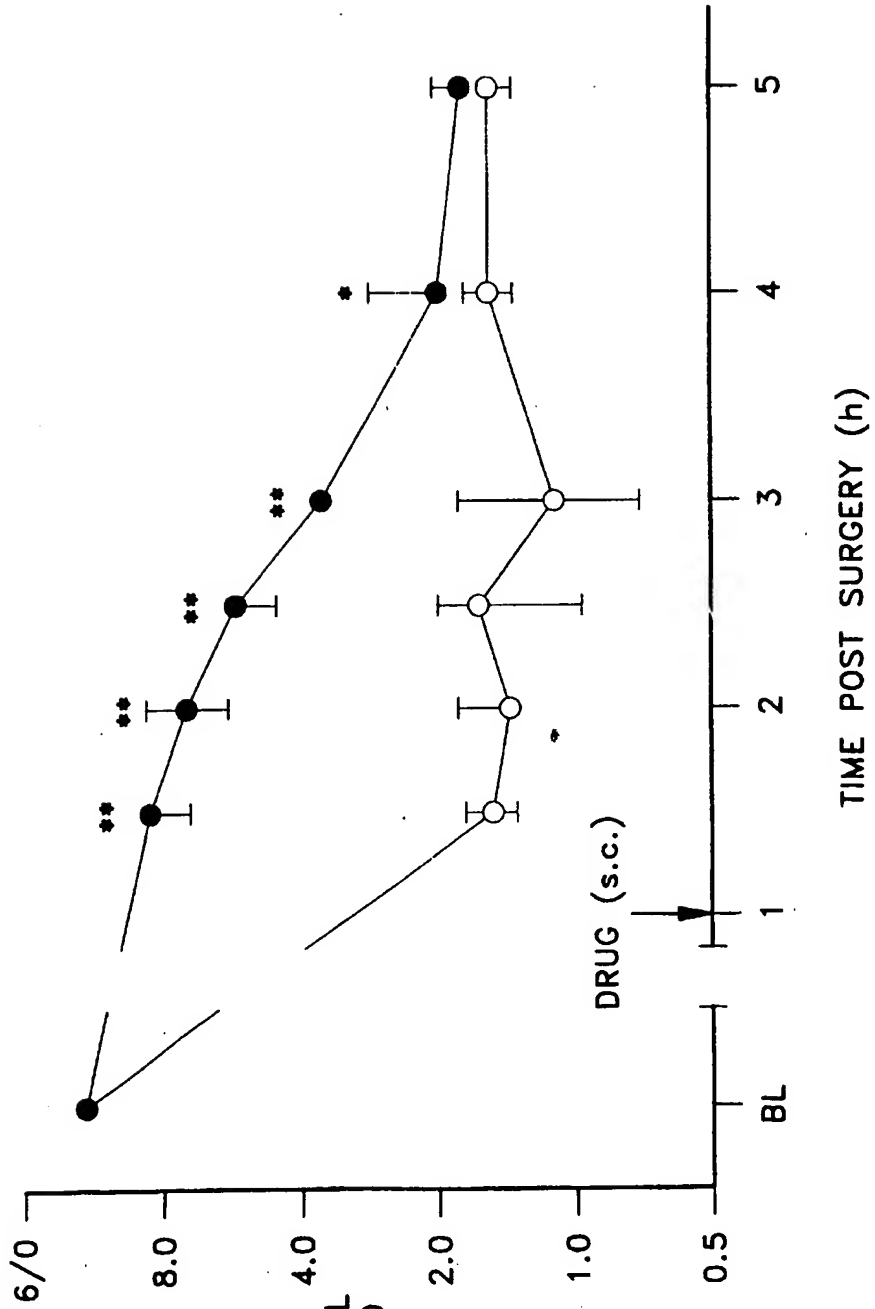


FIG-6b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0.5
WITHDRAWAL THRESHOLD (g)
BL
DRUG (s.c.)
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2
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4
5
TIME POST SURGERY (h)

INTERNATIONAL SEARCH REPORT

Inte onal Application No
PCT/US 97/12390

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/195

According to International Patent Classification(IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	G.A. MELLICK ET AL.: "Gabapentin in the management of reflex Sympathetic Dystrophy." J. PAIN SYMPTOM. MANAGEMENT, vol. 10, no. 4, 1995, pages 265-266, XP002043783 see the whole document ---	1,14
P,X	G.A. MELLICK ET AL.: "Reflex sympathetic dystrophy treated with gabapentin." ARCH. PHYS. MED. REHABIL., vol. 78, no. 1, 1997, pages 98-105, XP002043784 see the whole document ---	1,14

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[X] Further documents are listed in the continuation of box C.

[ ] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 November 1997	24/11/1997

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Klaver, T

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INTERNATIONAL SEARCH REPORT

Int. ational Application No
PCT/US 97/12390

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
P,X	M.J. FIELD ET AL.: "Gabapentin and S-(+)-3-isobutylgaba represent a novel class of selective antihyperalgesic agents." BR. .J. PHARMACOL., vol. 121, no. 8, 1997, pages 1513-1522, XP002043785 see the whole document	1-15

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

US006127418A

United States Patent [19]

Bueno et al.

[11] **Patent Number: 6,127,418**

[45] **Date of Patent: Oct. 3, 2000**

[54] **GABA ANALOGS TO PREVENT AND TREAT GASTROINTESTINAL DAMAGE**

[75] Inventors: **Lionel Bueno**, Aussonne; **Maria Chovet**, Montrouge; **Laurent Diop**, Saclay, all of France; **Antonio Guglietta**, Ann Arbor, Mich.; **Hilary J. Little**, County Durham, United Kingdom; **Michael Francis Rafferty**, Ann Arbor, Mich.; **Jiayuan Ren**, Oklahoma City, Okla.; **Charles Price Taylor, Jr.**, Chelsea, Mich.; **William P. Watson**, Meadowfield, United Kingdom

[73] Assignee: **Warner-Lambert Company**, Morris Plains, N.J.

[21] Appl. No.: **09/284,710**

[22] PCT Filed: **Aug. 18, 1998**

[86] PCT No.: **PCT/US98/17082**

§ 371 Date: **Apr. 19, 1999**

§ 102(e) Date: **Apr. 19, 1999**

[87] PCT Pub. No.: **WO99/08671**

PCT Pub. Date: **Feb. 25, 1999**

Related U.S. Application Data

[60] Provisional application No. 60/074,794, Feb. 16, 1998, and provisional application No. 60/056,753, Aug. 20, 1997.

[51] **Int. Cl.**[7] **A61K 31/195**

[52] **U.S. Cl.** **514/561**

[58] **Field of Search** 514/561

[56] **References Cited**

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Primary Examiner—Raymond Henley, III
Attorney, Agent, or Firm—Charles W. Ashbrook

[57] **ABSTRACT**

The present invention is directed to a method for preventing visceral and gastrointestinal damage such as gastric ulcers by administering a gamma-aminobutyric acid (GABA) analog and for treating gastrointestinal diseases such as inflammatory bowel disorders (IBD), functional bowel disorders (FBD) including dyspepsia and other visceral pain.

27 Claims, 9 Drawing Sheets

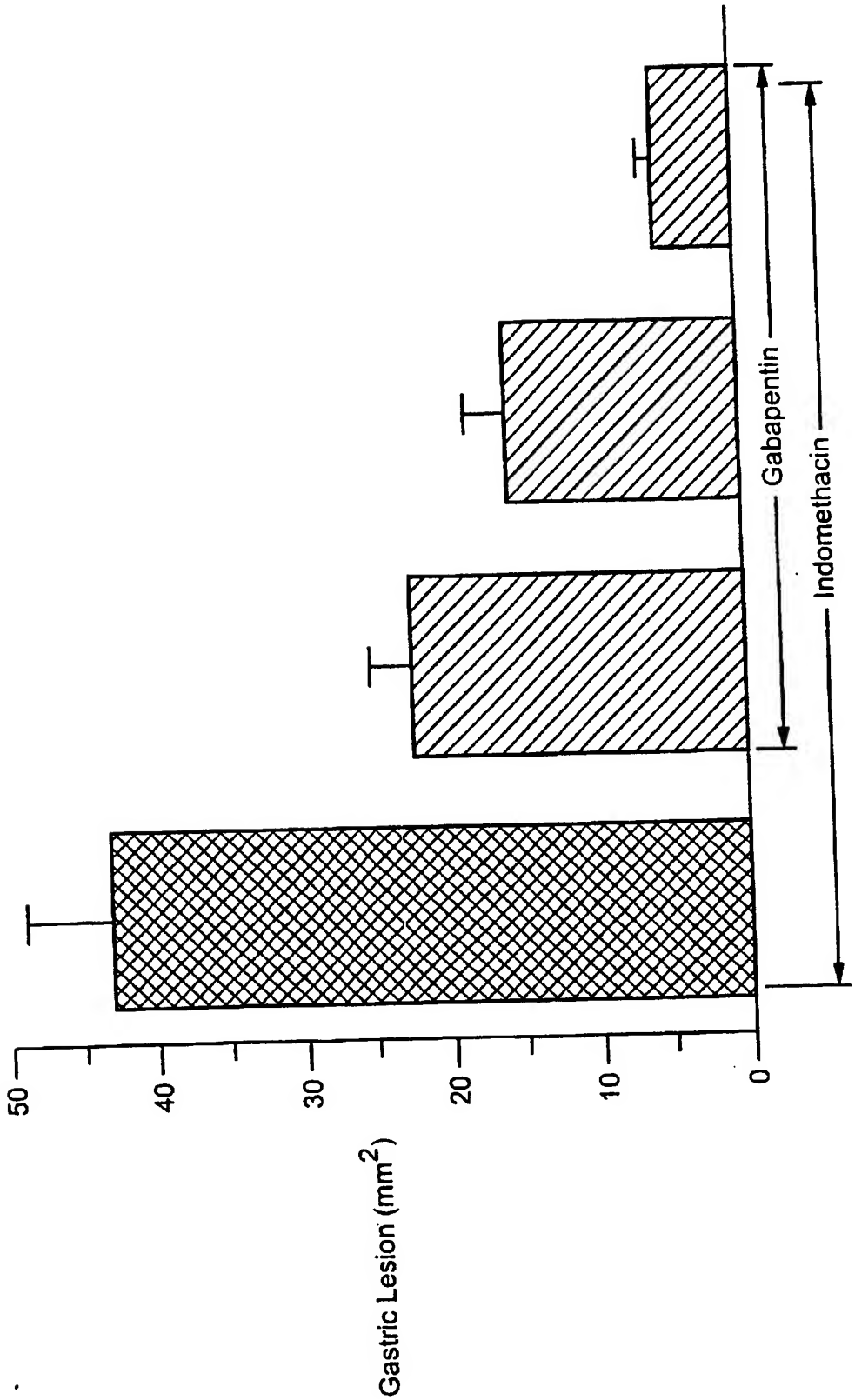


FIG-1

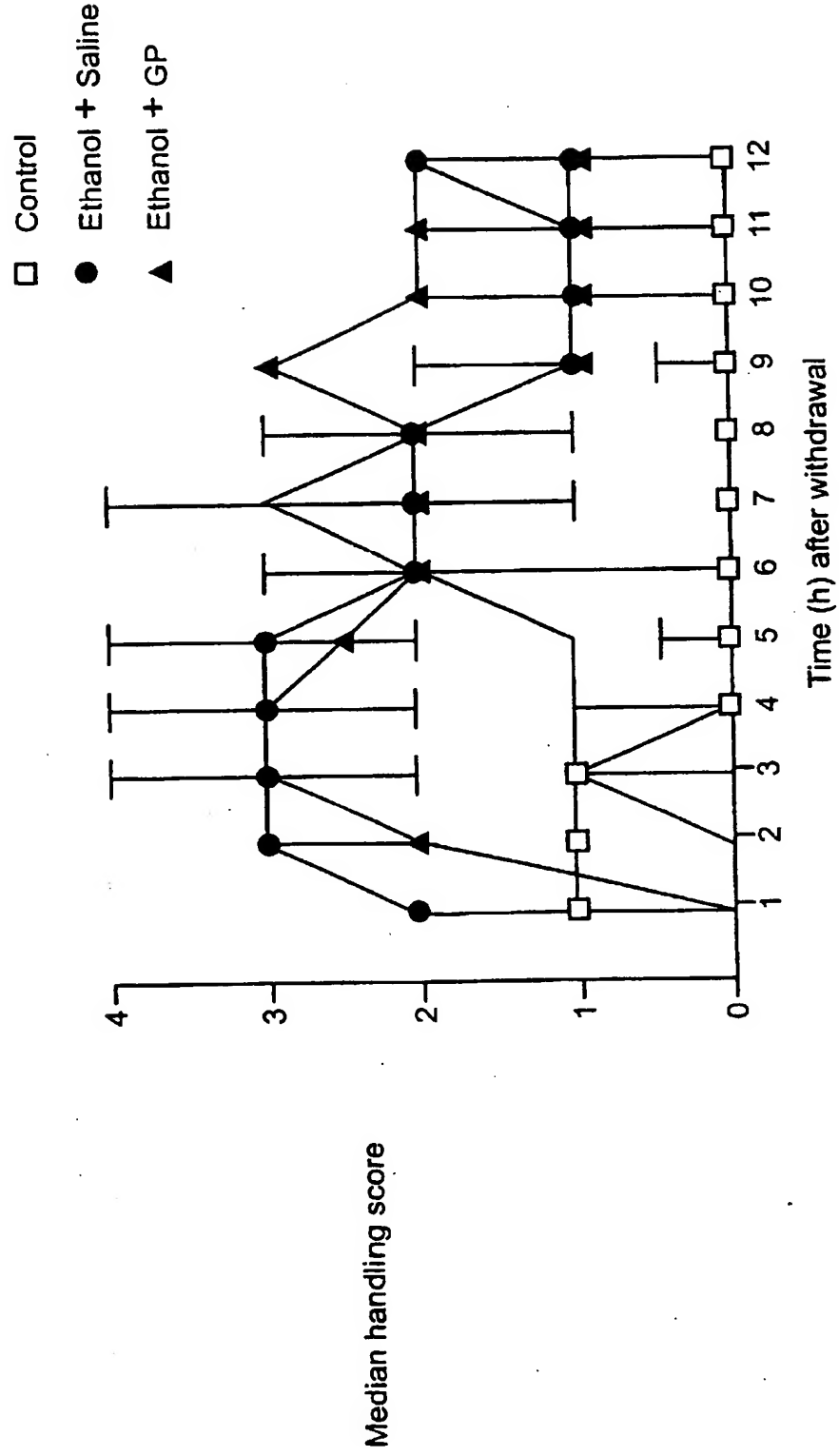

Control
Ethanol + Saline
Ethanol + GP
Median handling score
0
1
2
3
4
1
2
3
4
5
6
7
8
9
10
11
12
Time (h) after withdrawal

FIG-2a

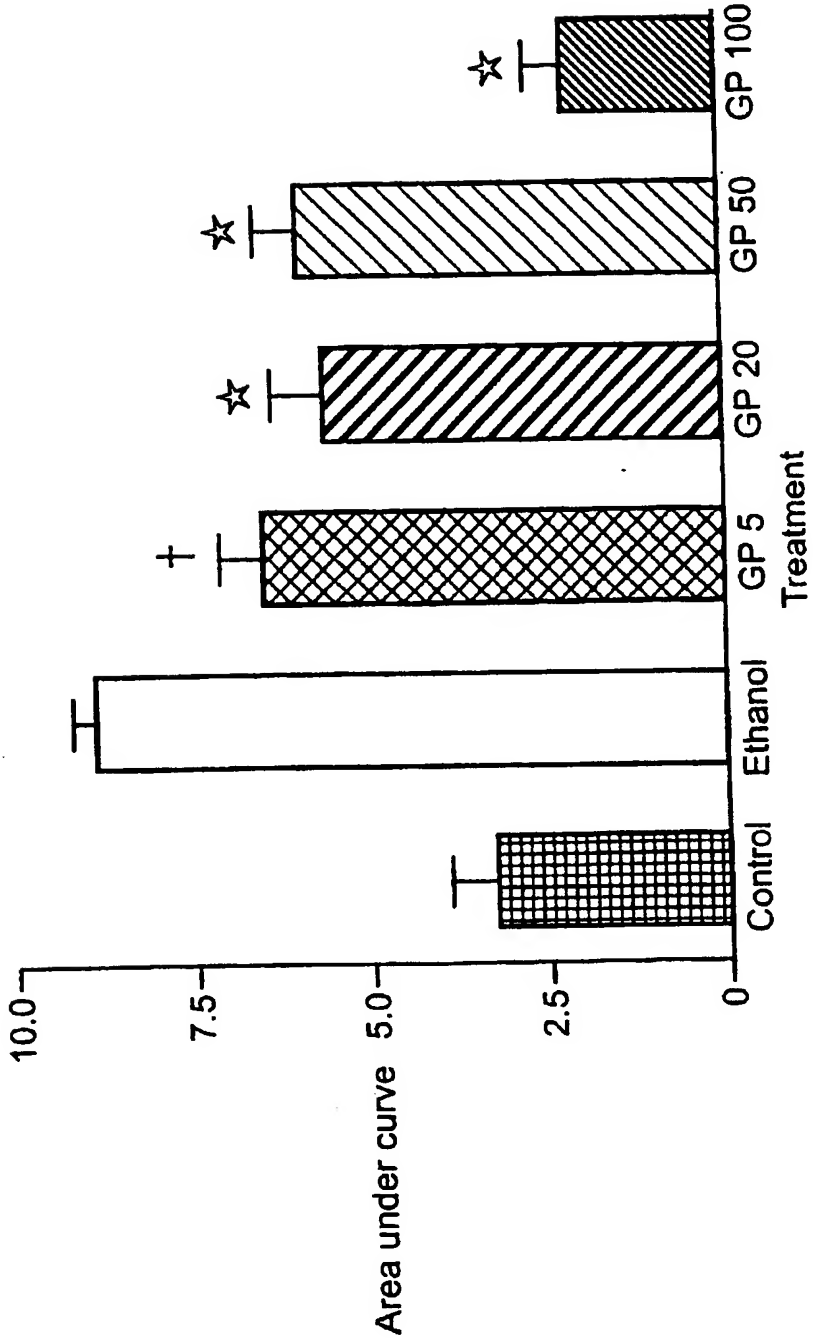

10.0
7.5
5.0
2.5
0
Area under curve
Control
Ethanol
GP 5
GP 20
GP 50
GP 100
Treatment

FIG-2b

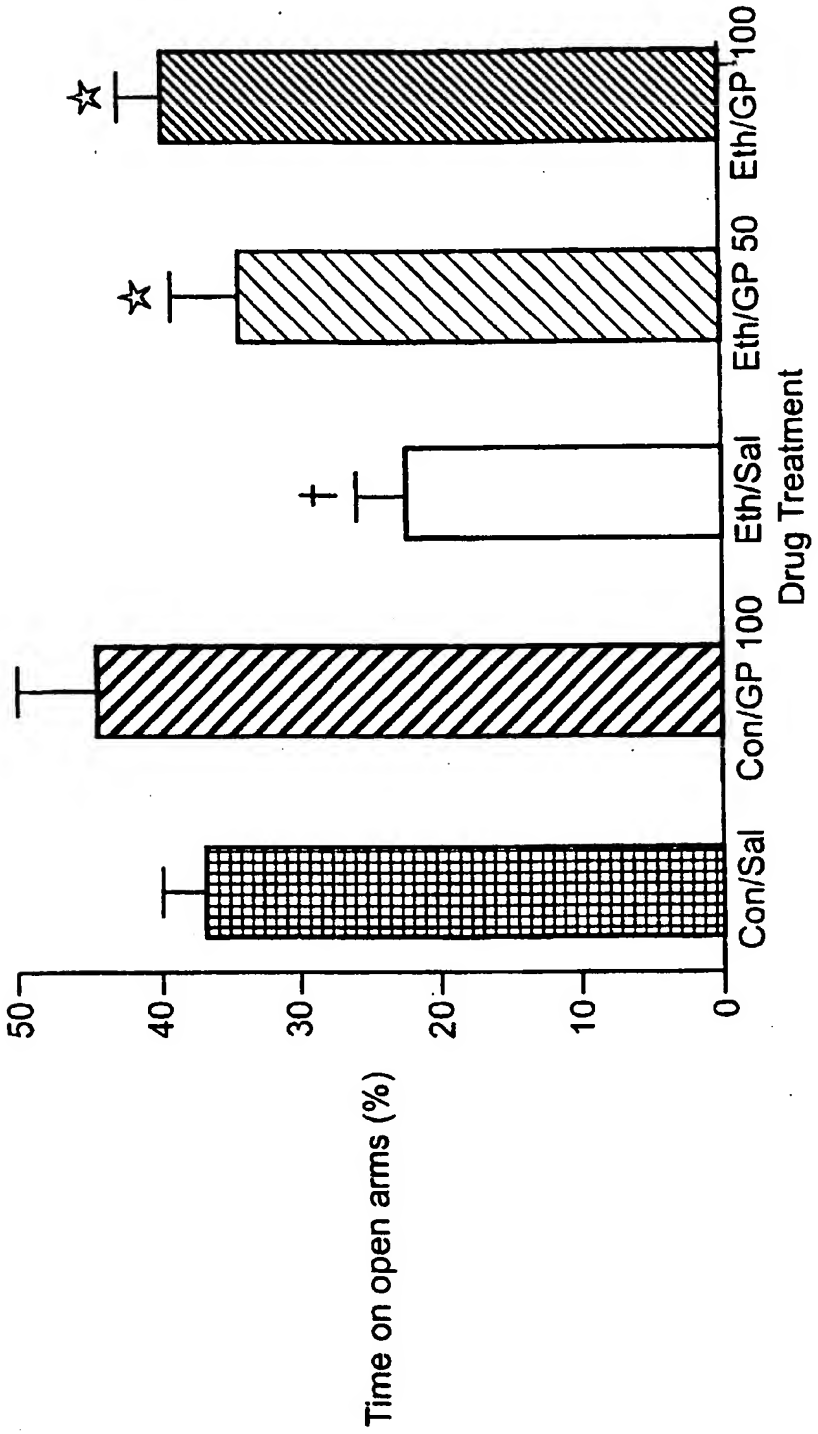

Time on open arms (%)
0
10
20
30
40
50
Con/Sal
Con/GP 100
Eth/Sal
Eth/GP 50
Eth/GP 100
Drug Treatment
*
*
+

FIG-3a

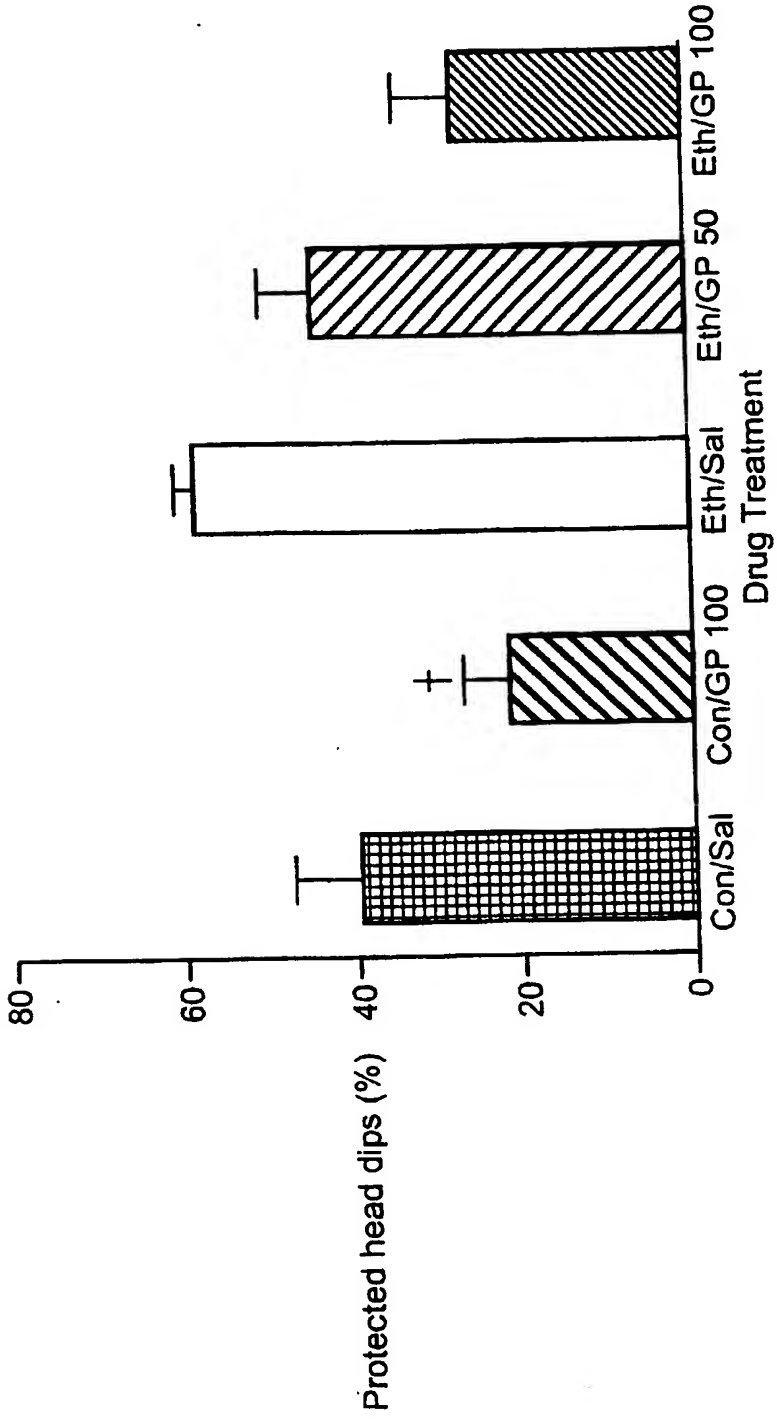

Protected head dips (%)
0
20
40
60
80
Con/Sal
Con/GP 100
Eth/Sal
Eth/GP 50
Eth/GP 100
Drug Treatment

FIG-3b

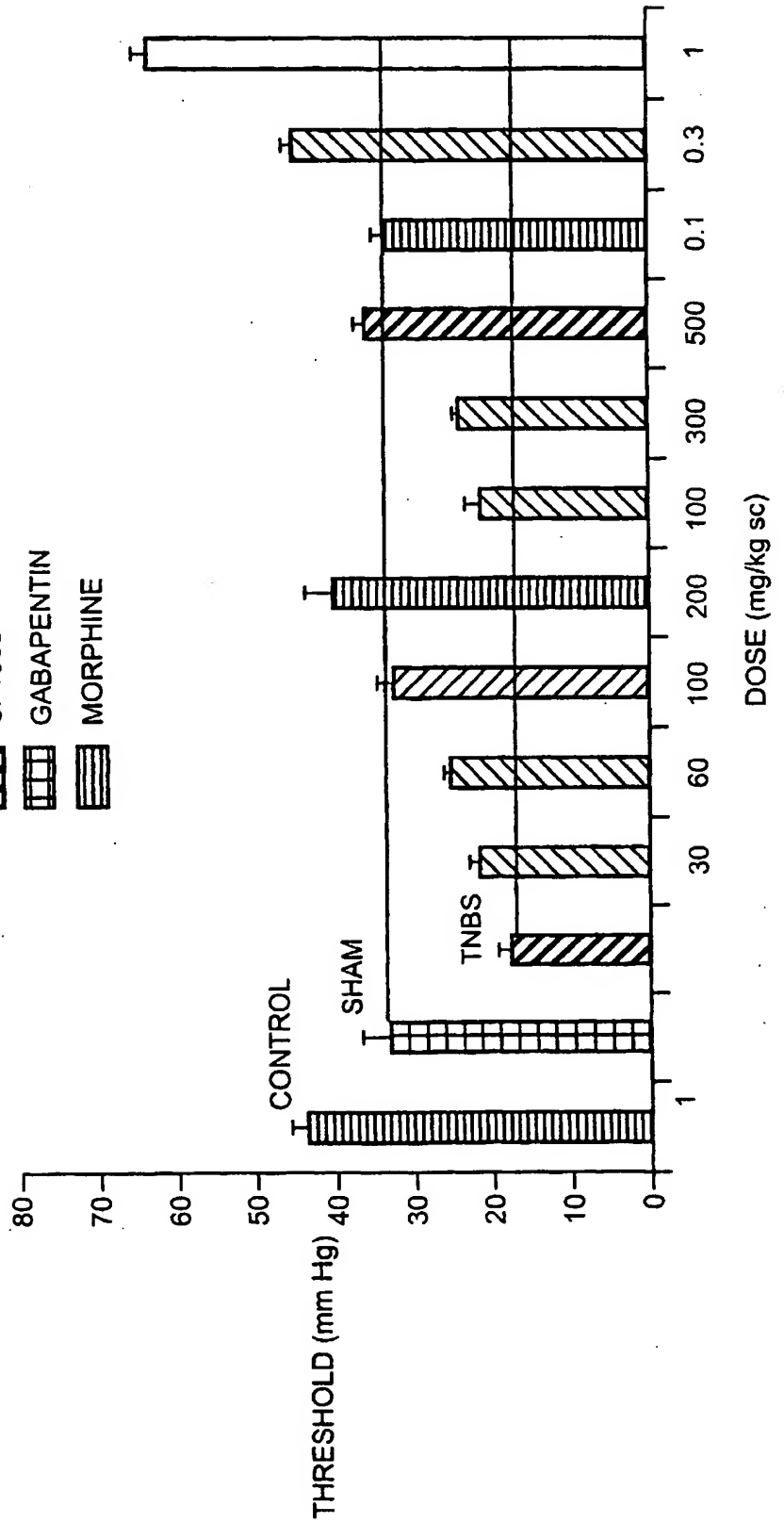

CI-1008
GABAPENTIN
MORPHINE
CONTROL
SHAM
TNBS
THRESHOLD (mm Hg)
0
10
20
30
40
50
60
70
80
1
30
60
100
200
100
300
500
0.1
0.3
1
DOSE (mg/kg sc)

FIG-4

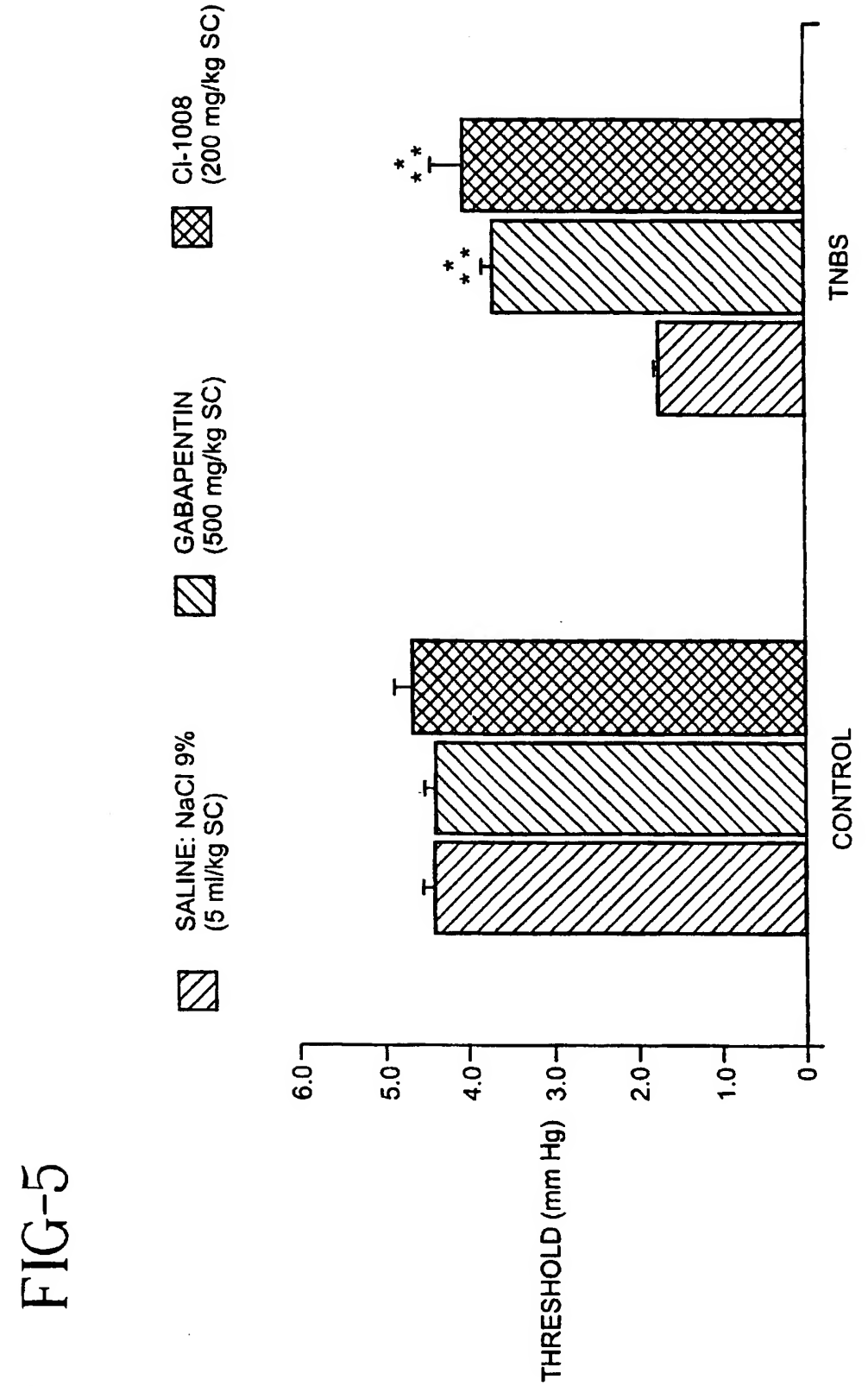

SALINE: NaCl 9%
(5 ml/kg SC)
GABAPENTIN
(500 mg/kg SC)
CI-1008
(200 mg/kg SC)
THRESHOLD (mm Hg)
6.0
5.0
4.0
3.0
2.0
1.0
0
CONTROL
TNBS
***
**

FIG-5

FIG-6 Gabapentin and Naproxen Mixtures Show Synergy in Rat Carrageenan Footpad Thermal Hyperalgesia

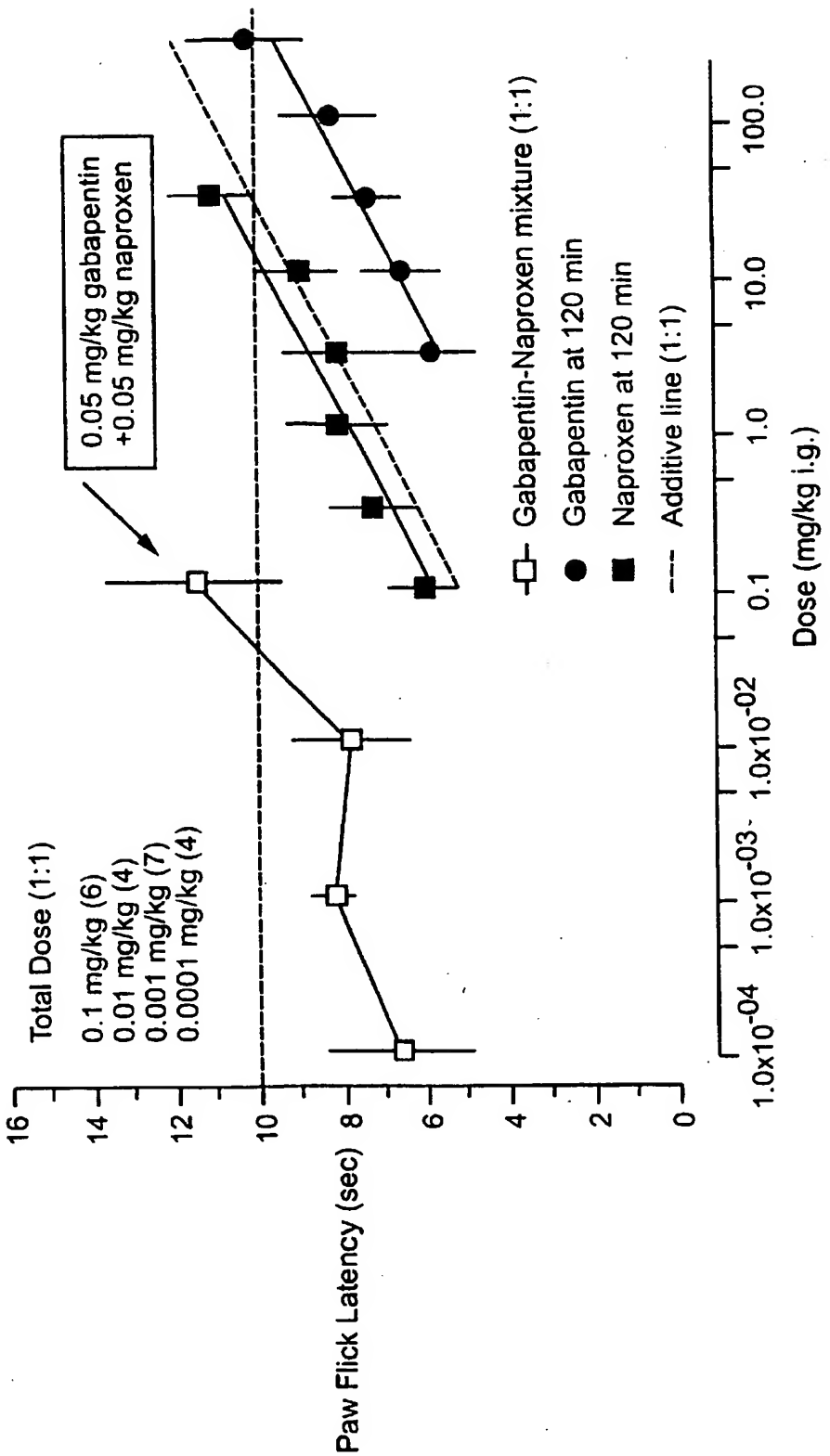
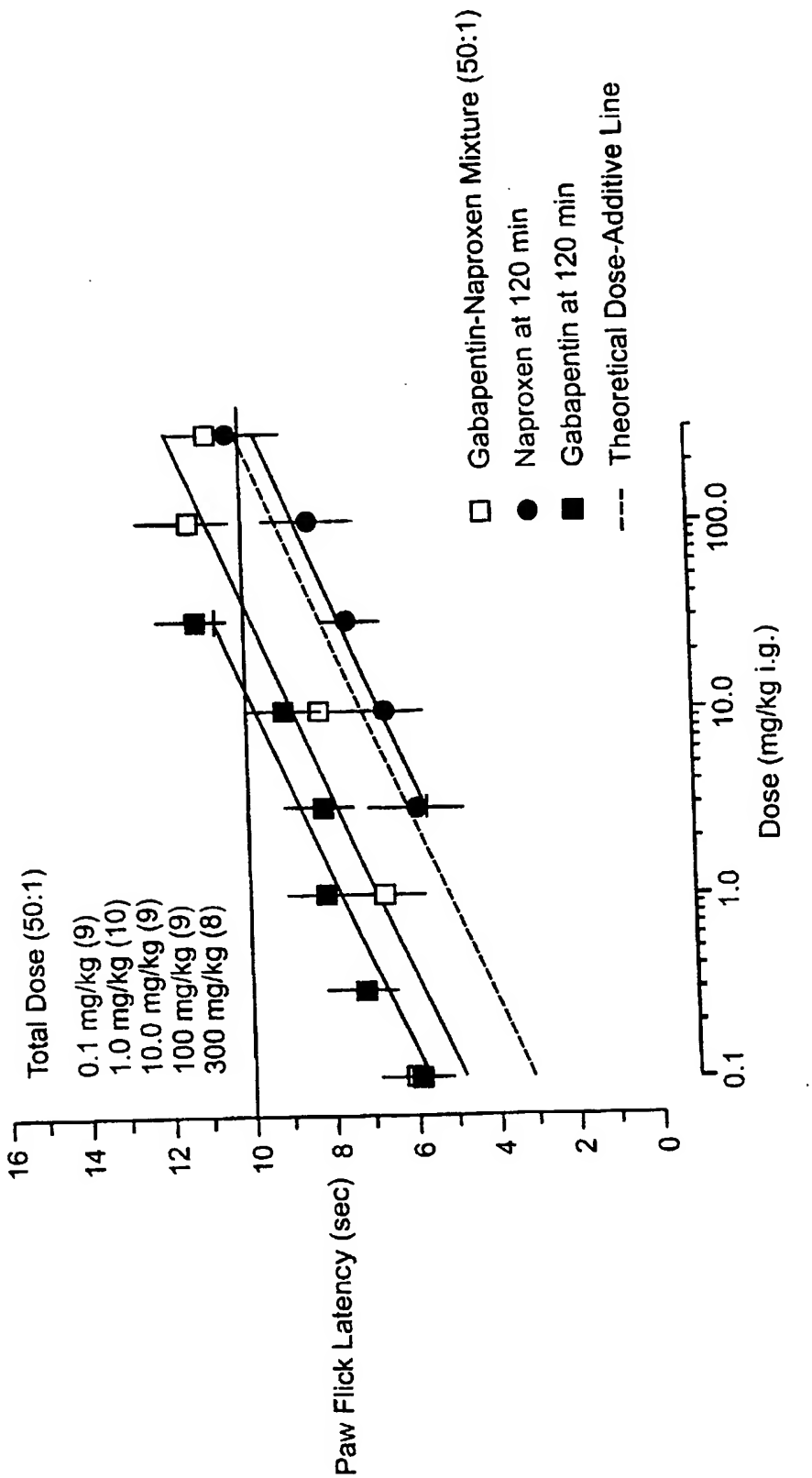


FIG-7 Gabapentin and Naproxen Mixtures Show Synergy in Rat Carrageenan Footpad Thermal Hyperalgesia



GABA ANALOGS TO PREVENT AND TREAT GASTROINTESTINAL DAMAGE

This application claims priority under 35 U.S.C. 119(e) over provisional applications 60/074,794 filed Feb. 16, 1998 and 60/056,753 filed Aug. 20, 1997, and is a 371 of PCT/US98/17082 filed Aug. 18, 1998.

FIELD OF THE INVENTION

This invention relates to a method for preventing visceral and gastrointestinal damage such as gastric ulcers by administering a gamma-aminobutyric acid (GABA) analog, and for treating gastrointestinal diseases such as inflammatory bowel disorders (IBD), functional bowel disorders (FBD), including dyspepsia and other visceral pain.

BACKGROUND OF THE INVENTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) are the most frequently prescribed drugs for the treatment of pain associated with osteoarthritis and many other musculoskeletal and inflammatory disorders. In the United States, about 100 million prescriptions are written each year to provide effective relief of pain and treatment of inflammatory diseases. Commonly used NSAIDs include sulindac, naproxen, indomethacin, mefenamic acid, diclofenac, fenoprofen, and diflunisal.

However, considerable evidence indicates that NSAIDs have frequent, serious, and costly gastrointestinal tract toxic side effects. These include mild dyspepsia, gastritis, peptic ulcer disease, as well as more serious gastrointestinal complications such as bleeding and perforation, leading sometimes to significant morbidity and, to a lesser extent, mortality. Serious GI complications due to NSAID use represent the greatest threat to life in patients with connective tissue diseases, second only to the primary disease and its complications. Similar gastrointestinal damage is caused by ingestion of alcohol. Indeed, a condition known as ethanol withdrawal syndrome is commonly encountered when prolonged ethanol consumption is terminated. In addition to gastrointestinal damage, this syndrome often results in tremors, anxiety, convulsions, hallucinations, and confusion.

Other commonly encountered gastrointestinal disorders include inflammatory bowel disorders (IBD) and functional bowel disorders (FBD), including dyspepsia. These GI disorders include a wide range of disease states that are currently only moderately controlled, including Crohn's disease, ileitis, ischemic bowel disease, and ulcerative colitis, as well as IBD, the irritable bowel syndrome, dyspepsia, and gastro-esophageal reflux for FBD, and other forms of visceral pain.

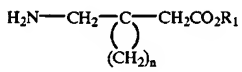
Gamma-aminobutyric acid has been shown to activate gastric afferent nerves which, in turn, have been shown to participate in gastric defense mechanisms. We have now discovered that GABA analogs dramatically reduce the gastrointestinal damage caused by drugs and alcohol. The GABA analogs also treat the conditions resulting from ethanol withdrawal syndrome, and GI disorders characterized as IBD and IBS.

All that is required to prevent gastrointestinal damage and to treat IBD, IBS, and alcoholism according to this invention is to administer to a subject who is in need of treatment an effective amount of a GABA analog.

Several GABA analogs are known. Gabapentin, a cyclic GABA analog, is now commercially available and extensively used clinically for treatment of epilepsy and neuropathic pain. Such compounds are described in U.S. Pat. No. 4,024,175. Another series of GABA analogs which are anti-seizure agents is described in U.S. Pat. No. 5,563,175.

SUMMARY OF THE INVENTION

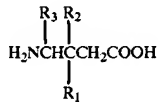
This invention provides a method for preventing and treating gastrointestinal damage and disorders comprising administering to a subject in need of treatment an effective amount of a GABA analog. A preferred embodiment utilizes a cyclic amino acid compound of Formula I



I

wherein R_1 is hydrogen or lower alkyl and n is an integer of from 4 to 6, and the pharmaceutically acceptable salts thereof. An especially preferred embodiment utilizes a compound of Formula I where R_1 is hydrogen and n is 5, which compound is 1-(aminomethyl)-cyclohexane acetic acid, known generically as gabapentin. Other preferred GABA analogs have Formula I wherein the cyclic ring is substituted, for example with alkyl such as methyl or ethyl. Typical compounds include (1-aminomethyl-3-methylcyclohexyl)acetic acid, (1-aminomethyl-3-methylcyclopentyl)acetic acid, and (1-aminomethyl-3,4-dimethylcyclopentyl)acetic acid.

In another embodiment, the method of the invention utilizes a GABA analog of Formula II



II

or a pharmaceutically acceptable salt thereof, wherein

R_1 is a straight or branched alkyl of from 1 to 6 carbon atoms, phenyl, or cycloalkyl of from 3 to 6 carbon atoms;

R_2 is hydrogen or methyl; and

R_3 is hydrogen, methyl, or carboxyl.

Diastereomers and enantiomers of compounds of Formula II can be utilized in the invention.

An especially preferred method of the invention employs a compound of Formula II where R_2 and R_3 are both hydrogen, and R_1 is $-(CH_2)_{0-2}-i\ C_4H_9$ as an (R), (S), or (R,S) isomer.

A more preferred embodiment of the invention utilizes 3-aminomethyl-5-methyl-hexanoic acid, and especially (S)-3-(aminomethyl)-5-methylhexanoic acid, now known generically as pregabalin, as well as CI-1008. Another preferred compound is 3-(1-aminoethyl)-5-methylhexanoic acid.

The invention additionally provides a composition comprised of an anti-inflammatory amount of an NSAID and a cytoprotective amount of a GABA analog.

DETAILED DESCRIPTION OF THE INVENTION

As noted above, the method of this invention utilizes any GABA analog. A GABA analog is any compound derived from or based upon gamma-aminobutyric acid. The compounds are readily available, either commercially, or by synthetic methodology well-known to those skilled in the art of organic chemistry. The preferred GABA analogs to be

utilized in the method of this invention are cyclic amino acids of Formula I. These are described in U.S. Pat. No. 4,024,175, which is incorporated herein by reference. Another preferred method utilizes the GABA analogs of Formula II, and these are described in U.S. Pat. No. 5,563,175 which is incorporated herein by reference.

All that is required to practice the method of preventing and treating gastrointestinal damage and disorders of this invention is to administer a GABA analog in an amount that is effective to prevent or treat the damage condition, i.e., to combat the effects of a NSAID or alcohol, or to control IBD and IBS. The invention includes a method for treating ethanol withdrawal syndrome and general alcoholism. The effective amount of GABA analog to be utilized will generally be from about 1 to about 300 mg per kg of subject body weight. Typical doses will be from about 10 to about 5000 mg per day for an adult subject of normal weight.

Typical "gastrointestinal damage" conditions caused by NSAID use include dyspepsia, gastritis, peptic ulcer, as well as lower gastrointestinal bleeding and perforation. Further effects of ethanol withdrawal syndrome include tremor, anxiety, and convulsions. Typical IBD conditions include ileitis, ulcerative colitis, and Crohn's disease.

Pharmaceutical compositions of the compound of the present invention or its salts are produced by formulating the active compound in dosage unit form with a pharmaceutical carrier. Some examples of dosage unit forms are tablets, capsules, pills, powders, aqueous and nonaqueous oral solutions and suspensions, and parenteral solutions packaged in containers containing either one or some larger number of dosage units and capable of being subdivided into individual doses. Some examples of suitable pharmaceutical carriers, including pharmaceutical diluents, are gelatin capsules; sugars such as lactose and sucrose; starches such as corn starch and potato starch, cellulose derivatives such as sodium carboxymethyl cellulose, ethyl cellulose, methyl cellulose, and cellulose acetate phthalate; gelatin; talc; stearic acid; magnesium stearate; vegetable oils such as peanut oil, cottonseed oil, sesame oil, olive oil, corn oil, and oil of theobroma; propylene glycol, glycerin; sorbitol; polyethylene glycol; water; agar; alginic acid; isotonic saline, and phosphate buffer solutions; as well as other compatible substances normally used in pharmaceutical formulations. The compositions of the invention can also contain other components such as coloring agents, flavoring agents, and/or preservatives. These materials, if present, are usually used in relatively small amounts. The compositions can, if desired, also contain other therapeutic agents. For use in combating the gastrointestinal effects of NSAIDs, the GABA analogs can be administered alone in unit dosage form, or in combination with the NSAID being utilized for the particular patient.

The percentage of the active ingredient in the foregoing compositions can be varied within wide limits, but for practical purposes it is preferably present in a concentration of at least 10% in a solid composition and at least 2% in a primary liquid composition. The most satisfactory compositions are those in which a much higher proportion of the active ingredient is present, for example, from 10% to 90% by weight.

Routes of administration of the subject compound or its salts are oral or parenteral. For example, a useful intravenous dose is between 5 and 50 mg and a useful oral dosage is between 20 and 800 mg. The dosage is within the dosing range used in treatment of gastrointestinal diseases such as ulcers and IBS, or as would be dictated by the needs of the patient as described by the physician.

A unit dosage form of the GABA analog to be used in this invention may also comprise other compounds useful in the therapy of gastrointestinal diseases.

The advantages of using the compounds of Formula I and II, especially gabapentin and pregabalin, in the instant invention include the relatively nontoxic nature of the compounds, the ease of preparation, the fact that the compounds are well-tolerated, and the ease of IV and oral administration of the drugs. Further, the drugs are not metabolized in the body to any great extent.

The subjects as used herein are mammals, including humans.

The invention also provides a composition comprising an NSAID (non-steroidal anti-inflammatory drug) together with a GABA analog. The NSAID will be present in an anti-inflammatory amount, preferably somewhat less than normally used, and the GABA analog will be present in a cytoprotective amount, namely an amount which will be effective in preventing or reducing the gastrointestinal damage otherwise caused by the NSAID. In general, the NSAID will be present for doses of about 10 to about 500 mg, and the GABA analog will be present at about 1 to about 1500 mg. Any NSAID can be combined with any GABA analog according to this invention. Preferred GABA analogs to be employed are the compounds of Formulas I and II, especially gabapentin and pregabalin. Preferred NSAIDs to be employed in the compositions include sulindac, naproxen, indomethacin, mefenamic acid, diclofenac, fenoprofen, diflunisal, etodolac, ibuprofen, piroxicam, acetylsalicylic acid, oxaprozin, and bromfenac. Most of the NSAIDs to be used are commercially available, generally as salts such as calcium, sodium, or potassium, for example, fensprofen calcium and bromfenac sodium. Especially preferred combinations include pregabalin or gabapentin, together with naproxen sodium or ibuprofen. The compositions may contain common pharmaceutical excipients such as those described above.

The ability of GABA analogs to treat gastrointestinal diseases according to this invention has been established in several animal models of induced gastric lesions and alcoholism.

BRIEF DESCRIPTION OF FIGURES

FIG. 1 shows the effect of gabapentin on gastric lesions caused by indomethacin.

FIG. 2 shows the effect of gabapentin on handling responses following withdrawal of chronic ethanol treatment.

FIG. 3 shows the effect of gabapentin on memory and drowsiness in animals receiving chronic ethanol treatment.

FIG. 4 shows the effects of gabapentin, CI-1008 (pregabalin), and morphine on colonic allodynia.

FIG. 5 shows the effects of gabapentin and CI-1008 on colonic pain threshold in rats.

FIGS. 6 and 7 show synergistic effects of gabapentin and naproxen mixtures.

EXAMPLE 1

Gabapentin was evaluated in animals to determine its ability to prevent gastric lesions otherwise caused by indomethacin.

Male Sprague-Dawley rats weighing 240 to 250 g were fasted for 24 hours and allowed free access to water prior to experiment. All test drugs were given intragastrically. Rats

were pretreated with different doses of gabapentin at doses of 40 and 60 mg. Thirty minutes later indomethacin (25 mg/kg) was administered. Another group of rats received 10 mg of gabapentin twice, 3 hours apart, followed by indomethacin administration. Three hours after indomethacin treatment, the rats were killed and gastric lesions were assessed. The severity of the lesions were determined by the measurement of the square area (mm^2) of visible lesions.

Results

1. Indomethacin caused severe gastric hemorrhagic injury; the areas of injury were measured at 42.6±5.2 mm^2 (mean,±standard error of mean).

2. Gabapentin pretreatment significantly reduced indomethacin-induced gastric injury. The gastric lesion with different doses of gabapentin pretreatment after indomethacin treatment were measured: 22.3±2.8 mm^2 with 40 mg, 16.5±2.2 mm^2 with 60 mg/kg, and 4.2±0.39 mm^2 with 10 mg twice.

3. Gabapentin pretreatment also dramatically reduced gastric bleeding.

The foregoing data are presented in FIG. 1, where the first bar is control (animals treated with indomethacin alone); Bar 2 is for animals treated with one dose of 40 mg of gabapentin; Bar 3 is for animals dosed one time with 60 mg of gabapentin; and Bar 4 is for animals dosed two times with 10 mg of gabapentin.

EXAMPLE 2

To determine the effects of gabapentin on ethanol-induced gastric lesions, rats were pretreated with 1 mL of 70% aq. ethanol (v/v), followed by gabapentin at a dose of 40 and 60 mg, respectively. Another group of rats were pretreated by 20 mg of gabapentin given twice, 3 hours apart, followed by ethanol administration. Thirty minutes later, all rats were killed and gastric lesions were assessed.

Results

1. Seventy percent ethanol induced significant gastric injury. The area of injury measured 41.9±3.7 mm^2.

2. Gabapentin pretreatment reduced ethanol-induced gastric injury. With 2 doses of 20 mg gabapentin pretreatment, the area of injury measured 2.1±0.3 mm^2. With 40 and 60 mg of gabapentin pretreatment, the area of injury measured 24.4±3.5 mm^2 and 18.7±2.2 mm^2, respectively.

EXAMPLE 3

The following test in rats was carried out to further establish the ability of gabapentin and Pregabalin to reduce the gastrointestinal damage caused by NSAIDS.

Animals

Male CD-Sprague-Dawley rats (132–202 g) were received and housed in a room with controlled temperature, humidity, and 12-hour light/dark cycle. After a period of acclimatization of 4 to 5 days, and after a 24-hour food fasting period, animals were used for the study described below.

Administration of GABA Analogs and Indomethacin

Gabapentin or pregabalin (CI-1008) were dissolved in water and administered orally at the following doses: 1, 10, 100, and 200 mg/kg in a volume of 1 mL. Control animals were dosed with an equal volume of vehicle (1 mL of water). Sixty minutes later, all the animals received 1 mL of a solution of indomethacin dissolved in 5% aqueous $NaHCO_3$ (80 mg/kg). Control animals received 1 mL of 5% aqueous $NaHCO_3$ orally. Experimental groups were as follows:

Group	Pretreatment	Damaging Agent
Group 1	Water	None ($NaHCO_3$)
Group 2	Water	Indomethacin 80 mg/kg
Group 3	Gabapentin 1 mg/kg	Indomethacin 80 mg/kg
Group 4	Gabapentin 10 mg/kg	Indomethacin 80 mg/kg
Group 5	Gabapentin 100 mg/kg	Indomethacin 80 mg/kg
Group 6	Gabapentin 200 mg/kg	Indomethacin 80 mg/kg
Group 7	Pregabalin 1 mg/kg	Indomethacin 80 mg/kg
Group 8	Pregabalin 10 mg/kg	Indomethacin 80 mg/kg
Group 9	Pregabalin 100 mg/kg	Indomethacin 80 mg/kg
Group 10	Pregabalin 200 mg/kg	Indomethacin 80 mg/kg

Evaluation of the Effect

Gastric damage caused by indomethacin correlates with inhibition of the cyclooxygenase product prostaglandin E2 (PGE_2). Animals were sacrificed by decapitation 4 hours post-indomethacin administration. The stomach was removed and opened along the greater curvature and its image digitized and stored on an optical disk using a 486-based PC computer equipped with CUE3 system imaging analysis software (Olympus Corp., Marietta, Ga., USA). Two 6-mm biopsies were taken from a constant region of the gastric mucosa located in each side of the glandular portion of the stomach, and their PGE_2 content was measured using a commercially available ELISA kit (Assay Designs Inc., Ann Arbor, Mich., USA). The presence of gastric damage was determined using the retrieved electronic image, and the extent of damage was measured using the CUE3 imaging software. Data are expressed as a percent of gastric area damaged and the PGE_2 content (pg/mL). The data are present below in Table 1.

TABLE 1

Compound	Drug Dose	N	% Area Damaged	PGE_2 Synthesis (pg/mL)
Control	NA	10	0.00 ± 0.00*	9525.27 ± 156.00*
Indomethacin ± Vehicle	NA	9	5.56 ± 0.48	1908.03 ± 72.31
Indomethacin ± Gabapentin	1 mg/kg	5	2.99 ± 0.46	1783.66 ± 73.47
Indomethacin ± Gabapentin	10 mg/kg	9	3.96 ± 0.35	3065.78 ± 137.19
Indomethacin ± Gabapentin	100 mg/kg	10	1.87 ± 0.1	2997.90 ± 226.80
Indomethacin ± Gabapentin	200 mg/kg	5	1.43 ± 0.40	2615.74 ± 165.36
Indomethacin ± CI-1008	1 mg/kg	4	8.07 ± 2.19	1209.95 ± 105.50
Indomethacin ± CI-1008	10 mg/kg	10	4.07 ± 0.42	2666.16 ± 307.45
Indomethacin ± CI-1008	100 mg/kg	10	1.99 ± 0.25*	3994.45 ± 318.95
Indomethacin ± CI-1008	200 mg/kg	5	0.34 ± 0.06*	3288.92 ± 407.43

Values are average ± standard error.
*$p < 0.05$ based on Kruskal-Wallis one-way analysis of variance followed by Dunn's test and compared to indomethacin group.

Both gabapentin and CI-1008 caused a reduction of the amount of gastric damage induced by indomethacin which, in the case of CI-1008, reached statistical significance at doses of 100 and 200 mg/kg.

As expected, the gastric damage caused by indomethacin was associated with a significant inhibition of the cyclooxygenase product PGE_2. Neither gabapentin nor CI-1008, at any dose tested, were able to significantly modify this effect. This data suggests that the significant reduction of the indomethacin-induced gastric damage caused by CI-1008 is

not related to an effect of this GABA analog on the cyclooxygenase enzyme.

The foregoing data establish that GABA analogs such as gabapentin and pregabalin are effective in preventing gastrointestinal damage such as gastric lesions, peptic ulcers, and even lower gastrointestinal bleeding, otherwise caused by consumption of alcohol or NSAIDs. The GABA analogs also treat the effects of alcohol withdrawal, which is a syndrome characterized by tremor, hallucinations, and confusion, and general gastrointestinal disorders such as IBD and IBS.

The following tests establish that GABA analogs are useful to treat ethanol withdrawal syndrome.

EXAMPLE 4

Male albino mice of the outbred TO strain (Bantin and Kingman, UK) were used in all studies. The weight ranged from 25 to 35 g, with no more than a 5 g range in any single experiment. The mice were housed, eight per cage, at 21° C.±1° C., with 55±10% relative humidity, and a 12-hour light/dark cycle with the light phase between 09:00 to 21:00. All mice received ad libitum access to tap water and standard laboratory chow (RM-1, Special Diet Services, UK) until their use in experiments or until their diet was replaced with a liquid diet.

Induction of Physical Dependence

Ethanol was administered in a liquid diet schedule. All mice received control diet for an initial 2-day period. Ethanol treated mice then received a diet containing 3.5% (v/v) ethanol/water for 2 days, followed by a diet containing 7% ethanol for a further 5 days. The average intake was 22 to 30 g/kg/day. Control groups were pair-fed a control diet, balanced isocalorifically to match the ethanol containing diet. There were no differences in the weights of the ethanol-treated and control mice at the end of the treatment periods. When mice were withdrawn from the ethanol (between 07:00 AM and 09:00 AM), they were provided with tap water until their use in experiments.

Drug Treatment

Gabapentin was dissolved in saline, the solution being made freshly each testing day. Intraperitoneal (i.p.) injections of either gabapentin, 10 mL/kg, or saline, were given immediately on withdrawal from the ethanol treatment in the studies on the handling responses, and 2 hours prior to measurement of audiogenic seizures. In the experiments using a standard elevated plus maze, gabapentin or saline was injected i.p. at 8 hours after the removal of the ethanol diet, and the mice were placed on the plus maze 60 minutes after the injections. In the studies on motor co-ordination (ataxia) and on locomotor activity, gabapentin or saline was injected into ethanol-naive chow fed mice immediately before testing. Measurements were then made for 60 minutes for the ataxia study, and for 30 minutes in the case of the locomotor activity.

Measurement of Handling-Induced Behavior

Following withdrawal from the ethanol treatment at 09:00 AM, ratings of handling-induced behavior were assessed by the same experimenter, on the same mice, every hour for a period of 12 hours after withdrawal from ethanol. Numerical ratings have the definitions shown in Table 2.

TABLE 2

Behavioral Ratings During Gentle Handling	
1	Mild tremor on lifting and turning
2	Continuous severe tremor on lifting and turning
3	Clonic forelimb extensor spasm on lifting
4	Clonic forelimb extensor spasm on lifting, which continued after placing mouse on cage top
5	Spontaneous evidence of myoclonic activity followed by (4)

Each mouse was lifted gently by the tail and held for 3 seconds, 30 cm under an "Anglepoise lamp" with a 60-watt bulb. The animal was gently rotated and its ensuing behavior rated on a scale of 1 to 5 according to the criteria in Table 2. Groups of 15 mice were used in each of the treatment groups, and the data were calculated as medians with interquartile ranges. The data were also expressed as the area under the curve at 4 and 12 hours from the withdrawal of the ethanol treatment. The results are shown in FIG. 2.

Elicitation of Audiogenic Seizures

At 8 and 12 hours from ethanol withdrawal, the susceptibility to sound-induced convulsions was measured in separate groups of ten mice. Mice were tested individually in a sound-proof perspex box 30×30×30 cm containing an electric door-bell. The bell was rung for 2 minutes or until the first signs of convulsions. The number of mice which responded by wild-running and clonic convulsions was counted. The mice were humanely killed as soon as a full convulsion was seen.

Anxiety-Related Behavior

Mice were withdrawn from the ethanol diet at 7:00 AM and tested for anxiety-related behavior 8 hours later using a murine elevated plus-maze. It was constructed of perspex with two opposing open arms (30×5×0.25 cm) and two opposing closed arms (30×5×15 cm) which extended from a central platform (5×5 cm). The floor was of matt black perspex. The animals were acclimatized to the experimental room 1 hour prior to experimentation. Experiments were conducted under dim red light, and each 5 minute session was video-taped for later analysis, by an observer unaware of the prior treatment. During this analysis (Observer 3.0, Noldus Information Technology, Wageningen, Netherlands) measurements were made of the time spent on each arm of the maze, the number of entries onto each arm and rearing activity. The measurements were made in accordance with the definitions in Table 3.

TABLE 3

Measurements of Behavior on the Elevated Plus Maze
Arm entry = All four paws onto either a closed or an open arm.
"Head Dip" = An exploratory forward head/shoulder movement over the side of an open arm and down towards the floor.
"Protected head dips" = Exploratory forward head/shoulder movement over the side of a closed arm and down towards the floor.
"Stretch-attend posture" = An exploratory flat body posture where the mouse stretches forward and then retracts to original position without moving forward.

Measurement of Ataxic Actions

Possible ataxic effects of gabapentin were studied in control animals (i.e., not treated with ethanol) by the rotorod method. Mice were placed on a rod rotating at 4.5 rpm, and the time they remained on the rod was measured automatically. A cut-off time of 180 seconds was used in all experiments. Before the acute drug injections, all mice were tested

on the rotorod to ensure that they stayed on for 180 seconds (a very small number did not do so and were excluded from the studies). Measurements were made for 60 minutes, at 10-minute intervals, after the acute administration of the drug under test. Eight mice were used in each treatment group.

Locomotor Activity

The effects of gabapentin in control animals were also tested on locomotor activity to determine the selectivity of the effects in the withdrawal studies. Mice were injected with gabapentin solution or saline and placed immediately in activity test cages crossed by infra-red beams. The number of infra-red beam breaks was measured every 5 minutes for the next 30 minutes. Rearing activity was measured by a similar set of infrared beams situated 4 cm above the cage floor.

Statistical Analysis

The results of the handling response ratings were compared by nonparametric two-way analysis of variance, designed for repeat measures on the same animal. The results of the area under the curve calculations were compared by the Mann-Whitney U-test. The convulsion incidence was analyzed by Fisher's exact probability test. The measurements from the elevated plus maze were subjected to one-way analysis of variance, followed by a Bonuferroni multiple comparison test, comparing all groups to the control group which received saline injections, and also comparing both ethanol treated groups which received gabapentin to the ethanol treated group which received saline. The ataxia measurements were analyzed by the Mann-Whitney U-test and the locomotor activity by Student's t-test.

RESULTS

Handling Response

The ratings of behavior in response to gentle handling showed the expected increase following withdrawal from the ethanol treatment. Gabapentin (GP), at 100 mg/kg (FIG. 2*a*), significantly reduced this increase in ratings when the results were compared over the 12-hour testing period ($p<0.001$). The effect of this dose of gabapentin showed a marked reduction in handling scores for around 4 hours. This time period was therefore used in later analysis to examine the area under the handling curve with each dose of the drug. The effects of lower doses of gabapentin were not significant over the 12-hour period of measurement, but when the areas under the curve were calculated for the first 4 hours of the study (FIG. 2*b*), significant effects of the 20- and 50-mg/kg doses were seen ($p<0.05$), as well as the 100-mg/kg dose ($p<0.01$).

Audiogenic Seizures

At the 8-hour time interval, 50 and 100 mg/kg gabapentin decreased the convulsion incidence after the audiogenic stimulus, with the 100-mg/kg dose reaching statistical significance ($p<0.05$). There was no effect of the lower doses (Table 4). No effect was seen of any of the doses tested at 12 hours from the end of the ethanol treatment (data not shown).

TABLE 4

The Effect of Gabapentin on Audiogenic Convulsions Measured 8 Hours From Ethanol Withdrawal

Chronic Treatment	Acute Injection	Percentage of Group Showing Clonic Convulsions
Control Diet	Saline	0
Ethanol Diet	Saline	80* $p < 0.05$ c.f. Control/Saline group
Ethanol Diet	Gabapentin 5 mg/kg	92
Ethanol Diet	Gabapentin 20 mg/kg	70
Ethanol Diet	Gabapentin 50 mg/kg	40
Ethanol Diet	Gabapentin 100 mg/kg	30 $p < 0.01$ c.f. Ethanol/Saline group

Elevated Plus Maze

The most prominent effect of ethanol withdrawal in this test was a decrease in the percentage time spent on the open arms of the maze (FIG. 3*a*, $F(4,50)=5.12$, $p<0.002$). Gabapentin decreased this effect at both 50 and 100 mg/kg. The p values were $p<0.05$ for the 50-mg/kg dose and $p<0.01$ for 100 mg/kg, for comparison with saline administration in both cases.

Mice undergoing ethanol withdrawal also showed a significant increase in head dips from the closed arms (protected head dips). This effect was significantly reduced by gabapentin at 100 mg/kg ($p<0.01$ compared with the effects of saline), as illustrated in FIG. 3*b* ($F(4,50)=6.53$, $p<0.001$). In control animals, the number of protected head dips was significantly decreased by gabapentin at 100 mg/kg ($p<0.05$, compared with control values after saline administration). Although the mean time on the open arms was increased in control animals after this dose of gabapentin, this was not significantly different from controls with saline.

EXAMPLE 5

LPS-Colonic Hypersensitivity Assay

The GABA analogs also have been evaluated for their ability to control and treat gastrointestinal disorders characterized as IBD and IBS. The assay utilized to evaluate the GABA analogs measures the effects of compound on lipopolysaccharide-induced delayed rectal allodynia in rats. Intraperitoneal (IP) injections of the endotoxin lipopolysaccharide (LPS) are known to induce long-lasting hyperalgesia in somatic pain models. The following assay LPS-colonic hypersensitivity assay was designed to evaluate the effect of IP injections of LPS on pain visceral threshold in an experimental model of rectal distension.

Animal Preparation

Male Wistar rats weighing 250 to 350 g were surgically prepared for electromyography, according to a standard technique. Rats were anesthetized by i.p. injection of acepromazine and ketamine (Imalgene 1000, Rhône-Mérieux, Lyon, France) at doses of 0.6 and 120 mg/kg, respectively. Two groups of four electrodes of nichrome wire (60 cm length and 80 μm diameter) were implanted bilaterally in the abdominal external oblique musculature just superior to the inguinal ligament. Electrodes were exteriorized on the back of the neck and protected by a glass tube attached to the skin. Animals were individually housed in polypropylene cages and kept in a temperature-controlled room (21° C.). They were allowed free access to water and food (UAR pellets, Epinay, France).

Electromyographic Recording

Electromyographic recording began 5 days after surgery. The electrical activity of abdominal striated muscles was recorded with an electroencephalo-graph machine (Mini VIII, Alvar, Paris, France) using a short-time constant (0.03 sec) to remove low-frequency signals (<3 Hz) and a paper speed of 3.6 cm/minute.

Balloon Distension Procedure

Rats were placed in plastic tunnels (6 cm diameter; 25 cm length) where they could not move, escape or turn around, in order to prevent damage to the balloon. They are accustomized to this procedure for 3 or 4 days before rectal distension (RD) in order to minimize stress reaction during experiments. The animals were determined to be accustomed to the plastic tunnel using two criteria: (i) a behavioral component: when the animals tried to escape or turn around no more than one time per 5 minutes, (ii) the abdominal basal activity: when abdominal striated muscles exhibited less than five abdominal contractions per 5 minutes in the absence of distension. The balloon used for distension was an arterial embolectomy catheter (Fogarty, Edwards Laboratories, Inc., Santa Ana, USA). Rectal distension (RD) was performed by insertion of the balloon (2-mm diameter; 2-cm long) in the rectum, at 1 cm of the anus, the catheter being fixed at the tail. It was inflated progressively by steps of 0.4 mL, from 0 to 1.6 mL, each step of inflation lasting 5 minutes. To detect possible leakage, the volume of water introduced in the balloon was checked by complete removal with a syringe at the end of the distension period.

Experimental Protocol

In a first series of experiments, a group of 8 rats were submitted to gradual rectal distention. The animals were previously (30 minutes) treated by gabapentin at doses of 30 and 100 mg/kg IP or its vehicle (NaCl 9% aqueous).

In a second series of experiments, the same group of 8 rats received IP lipopolysaccharide (*E Coli,* serotype 0111:B4) or its vehicle, at a dose of 1 mg/kg IP, 1 hour after a control rectal distension. Then, RD was performed 12 hours after LPS injection and was preceded (30 minutes) by IP administration of gabapentin (30 mg/kg) or its vehicle (0.3 mL/rat).

Drugs

LPS was dissolved in saline (NaCl 9%). Intraperitoneal injection of vehicle was given in a volume of 0.3 mL. LPS was purchased from Sigma-Aldrich (St. Quentin Fallavier, France).

Statistical Analysis

Statistical analysis of the number of abdominal contractions occurring during each 5-minute period during RD was performed by one-way ANOVA followed by Student's paired t-test. Values were expressed as the mean±SEM, and differences were considered significant for $p<0.05$.

The results are presented in Tables 5 and 6, and establish that gabapentin is effective in reducing lower gastrointestinal disorders such as IBS.

TABLE 5

Effect of Gabapentin on Abdominal Response Induced by Rectal Distension (Number of abdominal contractions/5 minutes; mean ± SEM, n = 7-8, *p < 0.05, **p < 0.01, significantly different from vehicle; n % of reduction vs vehicle)

Volume of Distension	Vehicle (0.3 mL/rat)	Gabapentin (30 mg/kg)	Vehicle (0.3 mL/rat)	Gabapentin (100 mg/kg)
0.4 mL	4.4 ± 1.6	5.0 ± 2.1	3.9 ± 1.8	2.0 ± 1.4
0.8 mL	19.1 ± 2.8	10.6 ± 3.4** (-45%)	19.6 ± 2.3	7.6 ± 3.4** (-61.2%)
1.2 mL	23.4 ± 2.6	16.1 ± 2.3* (-31.2%)	19.1 ± 2.3	16.7 ± 2.9

TABLE 6

Effect of Gabapentin on LPS-Induced Delayed (12 Hours) Allodynia (Number of abdominal contractions/5 minutes; mean, ±SEM, n = 7-8, +p < 0.001, significantly different from "LPS/vehicle" value; n % of reduction vs "LPS/vehicle")

Volume of Distension	LPS (1 mg/kg) + Vehicle (0.3 mL/rat)	LPS (1 mg/kg) + Gabapentin (3.0 mg/kg)
0.4 mL	9.7 ± 1.0	0.7 ± 0.5 + (-92.8%)
0.8 mL	11.7 ± 1.2	11.9 ± 0.8
1.2 mL	23.5 ± 2.2	16.3 ± 3.2

The foregoing experiment was carried out with the GABA-analog pregabalin. Pregabalin, at 30 mg/kg, reduced the number of cramps at both distension volumes of 0.4 and 0.8 mL. When injected 120 minutes before rectal distension, pregabalin, at both 10 and 30 mg/kg, had a similar effect at all distension volumes. LPS enhanced the number of abdominal contractions at the volume of 0.4 mL (9.7±1.0 vs. 3.7±1.0) 12 hours after its administration. This effect was suppressed when animals received pregabalin (1.8±0.9 vs. 9.7±1.0) at 30 mg/kg 30 minutes prior to rectal distension. These results establish that pregabalin is effective in reducing basal rectal sensitivity and in blocking LPS-induced rectal allodynia in rats.

EXAMPLE 6

TNBS-Induced Allodynia

GABA analogs were evaluated in rats suffering from chronic visceral allodynia induced by trinitrobenzene sulfonic acid (TNBS). Injections of TNBS into the colon of animals have been found to induce chronic colitis. In humans, digestive disorders are often associated with visceral pain. In these pathologies, the visceral pain threshold is decreased, indicating a visceral hypersensitivity. Consequently, the following study was designed to evaluate the effect of injection of TNBS into the colon on visceral pain threshold in an experimental model of colonic distension.

Male Sprague-Dawley rats weighing 340 to 400 g were used in the study. The animals were housed three per cage in a regulated environment (20±1° C., 50±5% humidity, with light 8:00 AM to 8:00 PM). Under anethesia (ketamine 80 mg/kg i.p.; acepromazin 12 mg/kg i.p.), TNBS (50 mg/kg), or saline (1.5 mL/kg) was injected into the proximal colon (1 cm from the cecum). After the surgery, animals were individually housed in the regulated environment.

A balloon catheter (5–6 cm length) was inserted through the anus into the colon and kept in position (tip of balloon 5 cm from the anus) by taping the catheter to the base of the

tail. The balloon was progressively inflated by step of 5 mm Hg, from 0 to 75 mm Hg, each step of inflation lasting 30 seconds. Each cycle of colonic distension was controlled by a standard barostat. The threshold corresponds to the pressure which produced the first abdominal contraction, at which time the cycle of distension was discontinued. To determine the colonic threshold, four cycles of distension were performed on the same animal.

In a first series of experiments, a group of eight rats treated with saline were subjected to a colonic distension session.

In a second series, a group of eight rats treated with TNBS were subjected to a colonic distension session.

In a third series, a group of eight rats treated with TNBS received a subcutaneous (sc) injection of gabapentin or CI-1008 30 minutes prior to initiation of the colonic distension cycle.

All test compounds were dissolved in saline except TNBS. TNBS was dissolved in EtOH 30% (w/v). Subcutaneous injection of vehicle was given in a volume of 2 mg/kg.

Statistical significance between each group was determined using a one-way ANOVA followed by Student's unpaired t-test. Differences were considered statistically significant at $p<0.05$.

Pain threshold (pressure of distension inducing the first abdominal contraction) after distal colonic distension was determined at Day 7 in two groups of awake rats: control animals and TNBS-treated animals. A significant decrease in the pain threshold was observed in TNBS-treated animals. Inflammatory parameters (colon weight, area of hyperemia and necrosis and colonic myeloperoxidase content) were measured in the proximal colon at Day 7 after TNBS treatment. All the parameters were significantly increased except the area of necrosis.

Gabapentin (100, 300, and 500 mg/kg sc) and CI-1008 (30, 60, 100, and 200 mg/kg sc) were administered 30 minutes before colonic distension and measurement of the inflammatory parameters. Gabapentin inhibited in a dose-related manner the TNBS-induced colonic allodynia. At 500 mg/kg sc, gabapentin completely blocked the effect of TNBS on colonic pain. CI-1008 also showed a dose-related inhibition of the decrease in pain threshold. At 100 mg/kg, CI-1008 completely suppressed the allodynia induced by TNBS. Morphine (0.1 mg/kg sc) completely suppressed the TNBS-induced decrease in pain threshold after colonic distension (FIG. 4). In contrast, neither gabapentin nor CI-1008 inhibited the colonic inflammatory effect of TNBS in these experimental conditions.

In normal conditions (control animals), morphine (0.3 mg/kg sc) significantly increased the colonic pain threshold while, in the same conditions, neither gabapentin (500 mg/kg sc) nor CI-1008 (200 mg/kg sc) modified the colonic pain threshold (FIG. 5). The results are further shown in Tables 7 and 8.

TABLE 7

Effect of CI-1008, Gabapentin, and Morphine on TNBS-Induced Chronic Colonic Allodynia in Rats

Treatment	Colonic Threshold (mm Hg)		SEM	n	p
Control	43.39	±	1.98	8	
Sham	33.44	±	3.25	8	*

TABLE 7-continued

Effect of CI-1008, Gabapentin, and Morphine on TNBS-Induced Chronic Colonic Allodynia in Rats

Treatment	Colonic Threshold (mm Hg)		SEM	n	p
TNBS	17.81	±	1.27	8	***
CI-1008					
30 mg/kg sc	21.72	±	1.51	8	?
60 mg/kg sc	25.47	±	1.03	8	??
100 mg/kg sc	33.13	±	1.83	8	???
200 mg/kg sc	40.47	±	3.75	8	???
Gabapentin					
100 mg/kg sc	22.03	±	2.23	8	
300 mg/kg sc	24.69	±	1.27	8	?
500 mg/kg sc	36.88	±	1.46	8	???
Morphine					
0.1 mg/kg sc	34.22	±	1.72	8	???
0.3 mg/kg sc	46.09	±	1.43	8	???
1 mg/kg sc	64.84	±	1.88	8	???

* = $p < 0.05$, ** = $p < 0.01$, and *** = $p < 0.001$ vs control.
? = $p < 0.05$, ?? = $p < 0.01$, and ??? = $p < 0.001$ vs TNBS.

TABLE 8

Effect of CI-1008 and Gabapentin on Colonic Threshold in Normal Rats

Treatment	Colonic Threshold (mm Hg)		SEM	n	p
Control	43.33	±	1.23	6	
CI-1008 200 mg/kg sc	46.41	±	2.26	8	NS
Gabapentin 500 mg/kg sc	43.75	±	1.44	6	NS

NS = Not significant vs control.

The foregoing data establish that GABA analogs such as gabapentin and CI-1008 suppress TNBS-induced colonic allodynia, and are therefore effective in abnormal colonic hypersensitivity reflecting the chronic pain in IBS.

EXAMPLE 7

Formalin-Induced Inflammatory Colonic Pain

The GABA analogs were evaluated in another model to determine their effect on inflammatory visceral pain, including pancreatitis and intestinal cystitis.

Administration of formalin into the wall of the rat colon causes acute inflammation and visceral pain. The aim of this study was to evaluate the antinociceptive activity of gabapentin and CI-1008 in visceral pain induced by colonic intrapariental injection of formalin.

Adult female Sprague-Dawley rats weighing 240 to 260 g were used in the study. The animals were housed three per cage in a regulated environment (20±1° C., 50±5% humidity, with light 8:00 AM to 8:00 PM) prior to use in the test.

Each test animal was placed in a transparent plastic cage (27×43×28 cm) with a layer of wood shavings on the floor. Drinking water was available. Cages were placed in such a way that visual interaction between animals was avoided. A mirror was positioned behind each cage to improve the recording of behaviors. Each animal was initially allowed 20 minutes to get used to its surroundings. Anesthesia was then

achieved by using isofurane (starting 4%, then 1.5% in a mixture of 2:3 nitrous oxide and 1:3 oxygen). The animal was suspended by its tail, the rectum was gently emptied with a cotton-capped stalk, and a coloscope was inserted through the anus. This designed endoscope has a lateral slot that allows for puncture of the intestinal wall under visual control, using a 51-mm-long needle (26 ga), at about 35 mm from the anal margin. Injected solutions were either 50 μL 5% aq. formalin (v/v), or the same volume of isotonic saline. Animals were allowed to recover from anesthesia as soon as the injection was completed (about 1 minute), and the observation period was started and continued for 2 hours. Thirty minutes after the end of the observation test, an IV injection of Evans Blue (1%) was administered, and 30 minutes later the animal was sacrificed. The abdomen was opened. The injection site and the zone of diffusion of Evans Blue were recorded by image analysis software. Data from rats in which the spread of the dye was not restricted to the sigmoid wall were discarded.

As listed in increasing order of pain intensity, these behaviors were: (i) abdominal licking and nibbling (L), (ii) body stretching, i.e., backward extension of the hind limbs (B), (iii) contraction of the flanks, sometimes evolving to a stretching attitude (C), and (iv) whole body contraction, the rat standing with its back curved, occasionally further graded according to the duration of the given episode: W_1 for less than 30 seconds, W_2 between 30 seconds and 1 minute, and W_3 for more than 1 minute. Behaviors were recorded for each animal throughout the 2-hour test on individual charts. A pain score (S) was then calculated for each of the successive 15-minute periods, using the following formula:

$$S=1L+2B+3C+4W_1+5W_2+6W_3$$

whereby the pain score was proportional to (i) the number of episodes of each selected behavior, and (ii) the coefficient, from 1 to 6, attributed to the given behaviors.

All compounds were dissolved in saline. Subcutaneous injection of vehicle was given in a volume of 2.5 mg/kg. Formalin was purchased from Prolabo.

Statistical significance between each group was determined by using a one-way ANOVA followed by Student's unpaired t-test. Differences were considered statistically significant at $p<0.05$.

Hyperalgesia is induced by intramural injection of formalin (5%, 50 μL/rat) into the colonic wall in unfasted female Sprague-Dawley rats. Gabapentin and CI-1008 were tested at 100, 300, 500 and 100, 200 mg/kg sc, respectively. Gabapentin and CI-1008 significantly and dose-dependently decreased the pain score induced by intracolonic formalin. The maximal inhibitory effect was observed after 500 mg/kg of gabapentin and 200 mg/kg of CI-1008. The results are presented in Table 9.

This study establishes that GABA analogs exhibit an antinociceptive effect on intra-colonic formalin-induced pain, and thus are effective in treating IBD and IBS, and visceral pain, including pancreatitis and intestinal cystitis.

TABLE 9

Effect of Subcutaneous Injection of Gabapentin and CI-1008 on Inflammatory Colonic Pain Induced by Intramural Injection of Formalin 5%

Treatment	% Antinociception		SEM	n	p
CI-1008					
100 mg/kg sc	18.55	±	7.41	7	***
200 mg/kg sc	70.81	±	7.47	6	***
Gabapentin					
0.3 mg/kg sc	-7.73	±	10.43	3	NS
100 mg/kg sc	13.62	±	12.65	9	NS
300 mg/kg sc	55.07	±	9.98	6	***
500 mg/kg sc	88.01	±	16.96	6	***

*** =

NS = Not significant vs control.

The following examples further illustrate compositions provided by the invention which contain a GABA analog in combination with an NSAID.

EXAMPLE 8

Tablet Formulation	
Naproxen sodium	200 mg
Gabapentin	300 mg
Magnesium stearate	20 mg
Microcrystalline cellulose	100 mg
Povidone	100 mg
Talc	50 mg

The ingredients are blended to uniformity and pressed into a tablet. The tablets are administered from 1 to 3 times a day for treatment of inflammatory conditions such as rheumatoid arthritis, ankylosing spondylitis, osteoarthritis, bursitis, tendinitis, and acute gouty arthritis.

EXAMPLE 9

Capsule Formulation	
Fenoprofen calcium, USP	150 mg
Pregabalin	50 mg
Cellulose	100 mg
Gelatin	50 mg
Titanium dioxide	10 mg
Cornstarch	50 mg

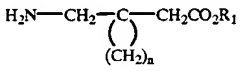
The ingredients are blended to uniformity and placed into a gelatin capsule. The capsules are administered from 1 to 4 times a day for treatment of rheumatoid arthritis and osteoarthritis. The combinations provided by this invention comprise an NSAID (eg, naproxen or meclofenamic acid) and a GABA analog (eg, pregabalin or gabapentin). Such combinations have been shown to be synergistic in their ability to treat pain. For example, gabapentin and naproxen sodium were combined in synergistic amounts and evaluated in a standard rat carrageenan footpad thermal hyperalgesia assay. This assay utilizes an extract of seaweed (carrageenan) that, when injected into the footpad of test animals, causes a sterile inflammation, thereby lowering the pain threshold. Analgesic agents, including GABA analogs such as gabapentin, raise the pain threshold back to normal, thereby enabling the animal to tolerate an external source of pain for a longer period of time relative to untreated control animals. Several fixed combinations of gabapentin and naproxen sodium, ranging in concentrations of about 50 parts by weight of GABA analog to 1 part by weight of NSAID, to

1:1 combinations, were evaluated in the foregoing assay. The results are shown in FIG. 6 (for fixed 1:1 combinations at various dosages) and in FIG. 7 (for fixed 50:1 combinations at various dosages). The data establish that the combinations of a GABA analog and an NSAID are synergistic in their ability to relieve acute and chronic pain and to induce analgesia.

What is claimed is:

1. A method for preventing and treating gastrointestinal damage and disorders comprising administering to a subject in need of treatment an effective amount of a GABA analog.

2. A method according to claim 1 employing a compound of Formula I



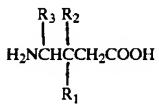
I

wherein R_1 is hydrogen or lower alkyl and n is an integer of from 4 to 6, and the pharmaceutically acceptable salts thereof.

3. The method according to claim 2 employing gabapentin.

4. The method according to claim 1 employing a compound selected from (1-aminomethyl-3-methylcyclohexyl) acetic acid, (1-aminomethyl-3-methylcyclopentyl)acetic acid, and (1-aminomethyl-3,4-dimethylcyclopentyl)acetic acid.

5. A method according to claim 1 employing a compound of Formula II



II

wherein R_1 is a straight or branched alkyl of from 1 to 6 carbon atoms, phenyl, or cycloalkyl of from 3 to 6 carbon atoms;

R_2 is hydrogen or methyl; and

R_3 is hydrogen, methyl, or carboxyl, and the pharmaceutically acceptable salts thereof.

6. The method according to claim 5 employing pregabalin.

7. The method according to claim 5 employing R-(3)-(aminomethyl)-5-methyl-hexanoic acid.

8. The method according to claim 5 employing 3-(1-aminoethyl)-5-methylhexanoic acid.

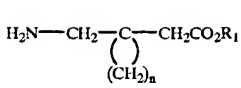
9. The method according to claim 1 wherein the gastrointestinal damage is in a subject who is receiving or will receive NSIAD therapy or alcohol.

10. The method according to claim 1 wherein the gastrointestinal damage is characterized as inflammatory bowel disorder or irritable bowel syndrome.

11. The method according to claim 1 wherein the condition treated is selected from Crohn's disease, ileitis, ischemic bowel disease, dyspepsia, and ulcerative colitis.

12. A method for treating ethanol withdrawal syndrome in a mammal in need of treatment comprising administering an effective amount of a GABA analog.

13. A method according to claim 12 employing a compound of Formula I

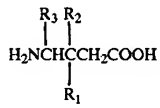


I

wherein R_1 is hydrogen or lower alkyl and n is an integer of from 4 to 6, and the pharmaceutically acceptable salts thereof.

14. The method according to claim 13 employing gabapentin.

15. A method according to claim 12 employing a compound of Formula II



II

wherein R_1 is a straight or branched alkyl of from 1 to 6 carbon atoms, phenyl, or cycloalkyl of from 3 to 6 carbon atoms;

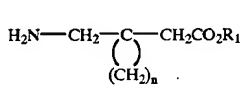
R_2 is hydrogen or methyl; and

R_3 is hydrogen, methyl, or carboxyl, and the pharmaceutically acceptable salts thereof.

16. The method according to claim 15 employing pregabalin.

17. A pharmaceutical composition comprising a GABA analog and a non-steroidal anti-inflammatory drug together with a pharmaceutically acceptable excipient, carrier, or diluent therefor.

18. A composition of claim 17 wherein the GABA-analog is a compound of Formula I



I

wherein R_1 is hydrogen or lower alkyl and n is an integer of from 4 to 6, and the pharmaceutically acceptable salts thereof.

19. The composition of claim 18 wherein the GABA analog is gabapentin.

20. A composition according to claim 17 wherein the GABA analog is a compound of Formula II.

21. The composition of claim 20 wherein the GABA analog is pregabalin.

22. A composition according to claim 17 wherein the non-steroidal anti-inflammatory drug is selected from sulindac, naproxen, indomethacin, mefenamic acid, diclofenac, fenoprofen, diflunisal, etodolac, ibuprofen, piroxicam, acetylsalicylic acid, oxaprozin, and bromfenac, or pharmaceutical salts thereof.

23. A composition according to claim 22 wherein the non-steroidal anti-inflammatory drug is selected from naproxen sodium, ibuprofen, or indomethacin.

24. A composition of claim 23 comprised of naproxen sodium and pregabalin.

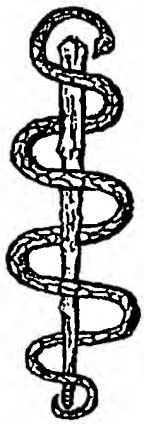
25. A composition of claim 23 comprised of naproxen sodium and gabapentin.

26. A composition of claim 23 comprising ibuprofen and pregabalin.

27. A composition of claim 23 comprising ibuprofen and gabapentin.

* * * * *

STEDMAN'S MEDICAL DICTIONARY



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densed to the amino group of its neighbor; occurs naturally in the anthrax bacillus capsule.

polyg'nathus [poly- + G. *gnathos*, jaw]. Unequal conjoined twins in which the parasite is attached to the jaw of the autosite.

polygraph (pol'ĭ-graf) [poly- + G. *graphō*, to write]. An instrument to obtain simultaneous tracings from several different pulsations; *e.g.*, radial and jugular pulse, apex beat of the heart.

Mackenzie's p., an instrument consisting of a system of tambours and a time-marker for recording simultaneously the jugular and arterial pulses and the apex beat. Used in the clinical investigation of cardiac arrhythmias.

polygyria (pol-ĭ-ji'rĭ-ah) [poly- + G. *gyros*, circle, gyre]. The presence of more than the usual number of convolutions on the surface of the brain.

polyhe'dral [poly- + G. *hedra*, seat, abode]. Having many sides or facets.

polyhidro'sis [poly- + G. *hidrōs*, sweat]. Hyperhidrosis.

polyhybrid (pol-ĭ-hi'brid). The offspring of parents differing from each other in more than three characters.

polyhydram'nios [poly- + G. *hydōr*, water, + amnion]. An excess in the amount of amniotic fluid.

polyhy'dric. Containing more than one hydroxyl group, as polyhydric alcohols or polyhydric acids. Glycerol, $C_3H_5(OH)_3$ is an example of the former; *o*-phosphoric acid, $OP(OH)_3$, an example of the latter.

polyhypermenorrhea (pol-ĭ-hi'pur-men-or-e'ah) [poly- + G. *hyper*, above, + *mēn*, month, + *rhoia*, flow]. Frequent and excessive menstruation.

polyhypomenorrhea (pol-ĭ-hi'po-men-or-re'ah) [poly- + G. *hypo*, below, + *mēn*, month, + *rhoia*, a flow]. Frequent but scanty menstruation.

polyidrosis. Hyperhidrosis.

polylep'tic [poly- + G. *lēpsis*, a seizing]. Denoting a disease occurring in many paroxysms, *e.g.*, malaria, epilepsy.

polylo'gia [poly- + G. *logos*, word]. Continuous and often incoherent speech.

polymas'tia [poly- + G. *mastos*, breast]. A condition in which, in the human, more than two breasts are present. Also called polymazia; hypermastia; multimaminae; pleomastia; pleomazia.

polymastigote (pol-ĭ-mas'tĭ-gōt). A mastigote having several flagella bunched together.

polyma'zia [poly- + G. *mazos*, breast]. Polymastia.

polyme'lia [poly- + G. *melos*, limb]. The presence of supernumerary limbs or parts of limbs.

polyme'lus. An individual exhibiting polymelia.

polymenorrhea (pol-ĭ-men-or-re'ah) [poly- + G. *mēn*, month, + *rhoia*, flow]. The occurrence of menstrual cycles of greater than usual frequency.

pol'ymer. A substance of high molecular weight, made up of a chain of identical, repeated "base units," sometimes mistakenly called "mers," whence *monomer*, *dimer*, *trimer*, etc., polymer. Starch may be considered a p. of glucose.

polymerase. Loosely, any enzyme catalyzing a polymerization, as of nucleotides to polynucleotides, thus belonging to EC Class 2, the transferases.

DNA p., see nucleotidyltransferase.

RNA p., see nucleotidyltransferase.

polymer'ic. Having the properties of a polymer.

polym'erid. Polymer.

pol'ymeriza'tion. A reaction in which a high molecular weight product is produced by successive additions or condensations of a simpler compound; *e.g.*, polystyrene may be produced from styrene, or rubber from isoprene, or a polynucleotide from a nucleotide.

polym'erize. To bring about polymerization.

pol'ymicro'bial. Polymicrobic.

polymicro'bic. Indicating an infection by several kinds of microorganisms.

pol'ymi'crolip'omato'sis [poly- + G. *mikros*, small, + *lipos*, fat, + *-oma* + *-osis*]. The occurrence of multiple, small, nodular, fairly discrete masses of lipid in the subcutaneous connective tissue.

polymitus (pŏ-lim'ĭ-tus) [poly- + G. *mitis*, thread]. Exflagellation.

pol'ymorph. Colloquial term for a polymorphonuclear leukocyte.

polymor'phic. Pleomorphic; multiform; occurring in more than one morphologic form; polymorphous.

polymor'phism [poly- + G. *morphē*, form]. Pleomorphism; occurrence in several forms; the existence in the same species or other natural group of several morphologic types.

lipoprotein p., heritable variations in low density β-lipoproteins; the variant lipoproteins exhibit different antigenic and chemical properties when compared with normal lipoproteins.

polymor'phocel'lular [poly- + G. *morphē*, form, + L. *cellula*, cell]. Relating to or formed of cells of several different kinds.

polymorphonuclear (pol'ĭ-mor-fo-nu'kle-ar) [G. *polymorphos*, multiform, + L. *nucleus*, kernel]. Having nuclei of varied forms; denoting a variety of leukocyte.

polymor'phous. Polymorphic.

polymyal'gia [poly- + G. *mys*, muscle, + *algos*, pain]. Pain in several muscle groups.

p. arterit'ica, p. rheumatica resulting from arteritis, especially disseminated giant cell arteritis.

p. rheumat'ica, a syndrome within the group of collagen diseases different from spondylarthritis or from humeral scapular periarthritis by the presence of an elevated sedimentation rate; much commoner in women than in men.

polymyoc'lonus. *Myoclonus multiplex.*

polymyositis (pol-ĭ-mi-o-si'tis) [poly- + G. *mys*, muscle, + suffix *-itis*, inflammation]. Inflammation of a number of voluntary muscles simultaneously.

polymyx'in. A mixture of antibiotic substances obtained from cultures of *Bacillus polymyxa* (*B. aerosporus*), an organism found in water and soils; p. is obtainable as a crystalline hydrochloride. There are five different p.'s, designated A, B, C, D, and E, which are about equally effective against Gram-negative bacteria, but differ in toxicity, p. E (colistin) and p. B being the least toxic. The p.'s are polypeptides containing various amino acids and a branched chain fatty acid, (+)-6-methyloctanoic acid. See also colistin sulfate and colistimethate sodium.

p. B. sulfate (USP, BP), Aerosporin; effective in tularemia, brucellosis, *Pseudomonas* infections, and urinary tract infections; but used systemically only for severe infections not responsive to less toxic agents; also used locally.

polyne'sic [poly- + G. *nēsos*, island]. Occurring in many separate foci; denoting certain forms of inflammation or infection.

polyneu'ral [poly- + G. *neuron*, nerve]. Relating to, supplied by, or affecting several nerves.

polyneuralgia (pol-ĭ-nu-ral'jĭ-ah). Neuralgia of several nerves simultaneously.

polyneu'ric. 1. Polyneural. 2. Relating to or containing many nerve cells.

polyneuritis (pol-ĭ-nu-ri'tis). Multiple *neuritis*.

chronic familial p., irritation of nerves related to infiltration by amyloid.

erythredema p., a chronic disease of childhood; vasomotor changes are constant.

infectious p., Guillain-Barré *syndrome*.

p. potato'rum, p. related to alcohol.

polyneuroni'tis. Inflammation of several groups of nerve cells; central *neuritis*.

polyneurop'athy [poly- + G. *neuron*, nerve, + *pathos*, disease]. A disease process involving a number of peripheral nerves.

buckthorn p., ascending p. resulting from ingestion of the fruit of *Karwinskia humboldtiana*, *q.v.*

polyneu'roradiculi'tis. Inflammation of several nerve roots and peripheral nerves.

polynuclear (pol-ĭ-nu'kle-ar). Multinuclear.

polynucleated (pol-ĭ-nu'kle-a-ted). Multinuclear.

polynucleo'sis. Multinucleosis; the presence of numbers of polynuclear, or multinuclear, cells in the peripheral blood.

polynucleotidase. Enzyme catalyzing the hydrolysis of polynucleotides to oligonucleotides or to mononucleotides. See phosphodiesterase, nuclease.

APPENDIX C

RELATED PROCEEDINGS APPENDIX

None